Stochastic Epidemic Models for Emerging Diseases

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Abstract

In this thesis several problems concerning the stochastic modelling of emerging infections are considered. Mathematical modelling is often the only available method of predicting the extent of an emerging disease and assessing proposed control measures, as there may be little or no available data on previous outbreaks. Only stochastic models capture the inherent randomness in disease transmission observed in real-life outbreaks, which can strongly influence the outcome of an emerging epidemic because case numbers will initially be small compared with the population size.

Chapter 2 considers a model for diseases in which some of the cases exhibit no symptoms and are therefore difficult to observe. Examples of such diseases include influenza, mumps and polio. This chapter investigates the problem of determining whether or not the epidemic has died out if a period containing no symptomatic individuals is observed.

When modelling interventions, it is realistic to include a delay between observing the presence of infection and the implementation of control measures. Chapter 3 quantifies the effect that the length of such a delay has on an epidemic amongst a population divided into households. As well as a constant delay, an exponentially distributed delay is also considered.

Chapter 4 develops a model for the spread of an emerging strain of influenza in humans. By considering the probability that an outbreak will be contained within a region in which an intervention strategy is active, it becomes possible to quantify and therefore compare the effectiveness of intervention strategies.

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Chapter 1

Introduction

1.1 Overview

This thesis aims to develop solutions to problems in the stochastic modelling of emerging diseases that are important from both a mathematical and a modelling point of view. Specifically, three problems are considered. Firstly, the problem of evaluating the conditional probability that an epidemic has died out given that no symptomatic cases have been observed, although asymptomatic cases may be present. Secondly, the effect on the behaviour of a households model of the length of the delay between discovering the presence of infection in a household and the implementation of an intervention. Finally, a model is developed for an emerging strain of influenza in humans in order to assess the risk that the disease escapes from a geographical region in which an intervention is effective.

This introductory chapter begins by providing a brief history of epidemic mod-

elling before describing the use of stochastic modelling for emerging diseases, with some relevant examples. Each research chapter is then described and related to other relevant research. Finally, some of the theory that will be relied upon throughout this thesis is explained and reviewed.

1.1.1 Foundations of epidemic modelling

This section describes the foundations and development of epidemic modelling, starting with an early model for smallpox.

Daniel Bernoulli (1760) was one of the first mathematicians to attempt to model the effects of disease in a population. He used a deterministic model to show that inoculation with a mild form of the smallpox virus would reduce the death rate of the population of France. An early reference to the non-linearity of epidemic models is made in a paper by Hamer (1906). Hamer postulated that the probability of an infection in the next period of time (in a discrete time model) was proportional to the number of infectious individuals multiplied by the number of susceptible individuals. This idea is called the mass action principle and has been used in many areas of science, in particular to determine the rate of chemical reactions, in work as early as Boyle's c. 1674 (Daley and Gani, 1999). Kermack and McKendrick (1927) incorporated this idea into the Deterministic General Epidemic Model.

One of the first epidemic models to incorporate the randomness observed in real-life outbreaks was suggested by McKendrick (1926). This model is a stochastic continuous time version of the Deterministic General Epidemic Model. Another early discrete-time model is the chain Binomial model of Reed and Frost (see

Bailey, 1975) in which the number of infectives to appear in the next time unit follows a binomial distribution, with the probability of infection dependent on the number of infectives in the current time unit. It was not until Bartlett (1949) studied McKendrick's model, that stochastic models in continuous time were examined more extensively. Since then, research has been directed towards the study of a wide variety of models, and their statistical analysis.

1.1.2 Stochastic modelling of emerging diseases

This section sets out the purpose of using mathematical modelling, particularly stochastic modelling, for emerging diseases and looks at some examples.

When a new disease emerges and begins to cause infections and fatalities it is desirable for health authorities to be able to make predictions concerning the future behaviour of the epidemic. Since the disease is emerging, there is unlikely to be a previous outbreak or other existing data on which to base predictions. Also, if there is no immunity in the population to this new pathogen, there is a risk that a very large outbreak will occur, causing a large number of deaths. Mathematical modelling is one of the few available tools for predicting possible outcomes, and assessing the effectiveness of proposed control strategies.

The spread of a disease through a population is inherently random due to the unpredictability of person-to-person contacts. It is particularly important to include this randomness in models for emerging diseases, as in the early stages of an outbreak case numbers will be very small and so random variations alone can cause an epidemic to die out.

There is a large amount of academic and public interest in emerging diseases.

Because of the randomness in disease spread and the potential for a disease to rapidly spread throughout the world via air travel, emerging infectious diseases are a global problem from their inception. Recent examples in humans include avian influenza, in particular the H5N1 subtype, Severe Acute Respiratory Syndrome (SARS) and the threat of bioterrorism.

Avian influenza is considered by the World Health Organisation to have a high risk of causing an imminent pandemic (Mills *et al.* 2006; Ferguson *et al.* 2005), and new cases in humans continue to be discovered (WHO, 2007). Many simulation based studies have attempted to predict the likely extent of an outbreak of pandemic avian influenza in humans and to assess the effectiveness of antiviral drugs in containing the spread. Ferguson *et al.* (2005) use a discrete time model with three levels of mixing, one of which is weighted according to the spatial distance between individuals. Their population structure is based on data for Thailand, and they use Markov Chain Monte Carlo methods on several influenza datasets to estimate suitable model parameters. They find that combining targeted antiviral prophylaxis with social distancing measures should be sufficient to prevent a pandemic, assuming that sufficient amounts of the antiviral drug have been stockpiled prior to the start of the pandemic. Longini *et al.* (2005) use a discrete time model with four levels of mixing to assess the use of different intervention strategies in rural Southeast Asia. They show that targeted use of antivirals would be sufficient to contain an outbreak with reproduction number below 1.4, as long as the intervention is applied within the first 21 days of the outbreak. The reproduction number can be thought of as the expected number of new cases to be generated by a typical infective, see section 1.5.4. They also consider the effect of pre-existing partial immunity in

the population caused by a vaccine poorly matched to the emerging strain.

SARS has been modelled in several studies to estimate the reproduction number and to attempt to understand the transmission dynamics so that intervention strategies can be improved. Riley *et al.* (2003) fit a stochastic model to data from the first 10 weeks of the outbreak and find a reproduction number of 2.7, excluding superspreader events in which one case generates a very large number of other cases. Lipsitch *et al.* (2003) fit a deterministic model to the same data and estimate the reproduction number to lie between 2.2 and 3.6. Anderson *et al.* (2004) provides a comprehensive review of the transition dynamics and control measures for SARS. Becker *et al.* (2005) take a more analytic approach. They calculate the effect on the threshold parameter of several proposed intervention measures for a two level mixing model based on a branching process of households, and use SARS as an example.

Several modelling studies have been carried out, aimed at assessing the effectiveness of the U.S. Center for Disease Control and Prevention (CDC) emergency response plan to a bioterrorist attack with smallpox. Kaplan *et al.* (2002) use a 17 state deterministic model that allows for asymptomatic infection, and has a queue for vaccinating at-risk individuals in an unstructured population. Halloran *et al.* (2002) simulate a discrete time stochastic model of a structured population with four levels of mixing. Both papers favour a mass vaccination policy over a targeted vaccination policy to halt a smallpox outbreak. Eubank *et al.* (2004) use a realistic social contact network to model the spread of smallpox and find that the vaccination strategy is largely irrelevant when compared with variations in the time taken to detect cases, and therefore a targeted vaccination policy is sufficient when combined with a fast response.

1.2 Asymptomatic carriers

This section motivates and describes chapter 2 of this thesis, before relating it to other relevant research.

Many diseases can be transmitted by infectious individuals that never develop symptoms or individuals that develop very mild symptoms, called asymptomatic carriers. Examples include influenza, mumps, rubella, cytomegalovirus, Epstein-Barr virus (which causes glandular fever) and polio. Clearly, asymptomatic infections are difficult to observe, and so if no cases are observed for a period of time the disease may still be present in the population. This chapter attempts to address this problem by calculating the probability the epidemic is over given a period in which no symptomatic cases have been observed. This is relevant to both emerging diseases like influenza, where the cases numbers are small, and diseases the World Health Organisation is attempting to eradicate, like polio.

In particular two probabilities are explored in this chapter. The first is the probability that the epidemic has died out at time t given that no cases have been observed in $(s, t]$. This is calculated for two models: a small population epidemic model and its large population branching process approximation. The second is the probability that the epidemic is over at the end of the first time period of length t in which no cases are observed. The same two models are considered, but for this second probability progress is difficult with the branching process approximation unless all of the cases are observed.

Little research has been done into this important area, although three papers tackle related problems.

Glass *et al.* (2007) apply Markov Chain Monte Carlo methods to a discrete time branching process model with two types of infectious individual: diagnosed and hidden. They obtain estimates of the distribution of the number of infectious individuals in the $(t+1)$th generation of the infection, given that the number of diagnosed individuals has been observed for the first t generations. Since it is necessary to know to which generation an infective belongs, the method of Glass *et al.* should only be used for data on the very early generations of infection. However, if the reproduction number is close to one, the highly stochastic first phase of an epidemic may last for many more generations than this. Chapter 2 assumes that the transmission parameters of the epidemic are already known, perhaps from previous outbreaks of the disease, or from similar diseases.

Eichner and Dietz (1996) simulate a continuous time Markov process model for the spread of polio with vaccination, in order to find the probability that the disease has died out given a case free period of length t. They calculate this probability by simulating the epidemic and recording the proportion of case free periods with length greater than t in which the disease has died out by the end. All of the simulations begin from a state of endemic polio in a completely unvaccinated population of 200,000 individuals. They find that a case free period of 3 years gives a 95% probability of eradication. Chapter 2 of this thesis uses a simpler Markov process model to the model used in Eichner and Dietz (1996), but instead of simulation methods, analytic results are derived where possible.

O'Neill and Roberts (1999) describe Markov Chain Monte Carlo methods for estimating the parameters for the Markov SIR epidemic model in which the removal times are observed until time t. The infection times can be considered

as missing data, and treated as model parameters. Since they do not assume that the epidemic is over at t, their method can be directly applied to give the probability the epidemic is over at t, given full knowledge of the removal process until that point in time. The information given by the process of removals is too complicated to make any analytic progress possible, so in chapter 2 of this thesis only the length of the period without discoveries is assumed to be known. Also, O'Neill and Roberts assume that every removal that occurs before t is observed, ignoring asymptomatic carriers.

Finally, note that the asymptomatic carriage epidemic model used in chapter 2 generalises the one first proposed by Downton (1968). To obtain Downton's model, set the infectious period of an infective individual to have zero length, so that they are instantly removed. Downton gives the distribution of the number of survivors in terms of a triangular system of equations. The joint distribution of the state probabilities and the severity for Downton's model is given in Ball and Clancy (1995). In chapter 2 the joint distribution of the state probabilities and the severity are found for the asymptomatic carriage epidemic model, thus generalising the work of Ball and Clancy (1995).

1.3 Modelling the effects of a delay in intervention

This section briefly motivates and describes chapter 3, before discussing a small number of relevant papers.

It is realistic to include in an epidemic model a delay between observing that an individual has been infected and the time at which an intervention can be applied to their household. Although many modelling papers include such a delay, the effect that the length of the delay has on the outcome of the epidemic is rarely investigated. Chapter 3 considers a model in which the time between the end of an individual's infectious period and the implementation of the intervention has a random length. Principally, two distributions are considered: the constant distribution and the exponential distribution. The effect of the mean length of the delay on the sum of the infectious periods is also explored. For epidemics amongst a population divided into households, such calculations are necessary to calculate the effect of the intervention on the reproduction number.

Ball *et al.* (2007) perform calculations similar to those seen in chapter 3 to calculate the effect of intervention strategies on the reproduction number for a model of an epidemic amongst a population divided into households. In their model individuals are observed at the end of their infectious period and there is no delay before the intervention is applied.

Longini *et al.* (2004) use a discrete time simulation model with four levels of mixing to predict the effectiveness of using antivirals to prevent an influenza

pandemic. They investigate the effect of including a delay before intervention, and they find that the intervention strategy remains effective for a delay of one to three days; there remain substantial benefits for a delay of four days, but any longer delay means that the intervention is ineffective. Section 3.10.3 attempts to produce the results of this simulation study analytically for a two level mixing model constructed to be analogous to the four level mixing model used by Longini *et al.* (2004).

Eubank *et al.* (2004) simulate a smallpox epidemic on a dynamic bipartite graph designed to capture a realistic contact structure in the population. They investigate the effect of a delay in response, and also allow infectious individuals to withdraw to the home. They find that the time taken to withdraw to the home has the strongest effect on the size of the outbreaks, followed by the delay in the response, and that the choice of vaccination strategy is much less important than these two considerations. This highlights the importance of investigating the effect of a delay in intervention on the outcomes of an epidemic.

1.4 Evaluating the probability of containment for pandemic influenza

Influenza has caused several pandemics in the past (Oxford, 2006), and is thought to be extremely likely to cause the next major pandemic (Mills *et al.*, 2006; Ferguson *et al.*, 2005). Consequently, there is a large literature on modelling outbreaks of an emerging strain of influenza and possible strategies to control such outbreaks. This section describes the approach of chapter 4 and then relates it to a small selection of papers thought to be most relevant.

Threshold parameters like R_* (see section 1.5.4) can be used to assess the effectiveness of interventions. If an intervention reduces the threshold parameter below one, then the epidemic will die out with probability one. Many papers judge an intervention only to be effective if it reduces the threshold parameter below one, and not otherwise, see for example (Becker and Dietz, 1995; Ball *et al.*, 1997; Becker *et al.*, 2005). There are several problems with this approach: firstly it is very difficult to judge from the threshold parameter how long it will take for the disease to die out, or how many cases will be created. Also, it does not take into account the chance of the epidemic dying out despite the fact that the threshold parameter is greater than one. Finally, the intervention strategy will not be fully effective everywhere, and the threshold parameter does not take into account the probability that the disease will be transmitted to a region in which the surveillance is not as good, or the intervention cannot be applied as efficiently.

In order to provide an alternative to using the threshold parameter alone to assess intervention strategies, chapter 4 describes a method for calculating the

probability that the outbreak does not escape from a region in which the intervention is fully effective. This containment probability has several advantages. The first advantage is that probabilities are easier to interpret than threshold parameters. The containment probability also incorporates the probability that the epidemic dies out even if the threshold parameter is greater than one. Finally, the spread of the disease to another geographic region is explicitly modelled, clearly demonstrating the dependence of the model behaviour on the external contact rate. Chapter 4 develops a multitype branching process of household subepidemics to model the progression of the disease in a population where the intervention is effective; and models the transmission of the disease outside of this population with a Poisson process. The models for the household subepidemics are very flexible and can incorporate many different kinds of intervention.

Longini *et al.* (2005) use a discrete time simulation model to assess the effectiveness of using antiviral prophylaxis to contain emerging pandemic influenza at the source of the outbreak. They use four functions of the realisations of the epidemic model to assess the effectiveness and efficiency of eight intervention strategies. One of these functions is the expected number of individuals who leave the intervention region at any point during their infectious periods. They estimate the probability that on any day an individual will travel outside of the population of 500,000 to be 10^{-3}, and multiply this by the number of infectives each day. Chapter 4 improves upon this by calculating the probability that there are no infectious contacts to outside the population, which is easier to interpret than the expected number of escapees.

Ferguson *et al.* (2005) estimate the transmission parameters for pandemic in-

fluenza emerging in Southeast Asia. These parameters are then used in a simulation model for an emerging pandemic to estimate the probability of a large outbreak in Southeast Asia, which would cause a global pandemic. Interventions with social distancing measures and prophylactic use of antiviral drugs are also modelled. Ferguson *et al.* (2005) obtain explicit parameters for household transmission and antiviral efficacy. These parameters are applied to the branching process model in chapter 4 to compare the effectiveness of different intervention strategies.

1.5 Background theory

This section sets out some results concerning stochastic epidemic models that will be relied upon throughout this thesis. First, the SIR stochastic epidemic model will be defined, then a branching process approximation will be considered. Structured population models are then defined with particular reference to two level mixing household models. Finally, threshold parameters for these models are explored.

1.5.1 The SIR stochastic epidemic model

The standard SIR (Susceptible Infective Removed) epidemic model is a well studied model for the spread of an infectious disease through a fixed population. This section sets out to carefully construct the model, and then generalise it to have multiple types of individual. For more details see Andersson and Britton (2000).

Consider a closed, homogeneous and homogeneously mixing population of individuals partitioned at any time $t \geq 0$ into three categories: susceptible, infective and removed. Susceptible individuals become infectives when they come into contact with an infective. It is assumed that the newly infected individual undergoes no latent period (during which they are infected but not infectious) but instead, instantly begins their infectious period. When their infectious period is over, an infective moves into the removed category - they are either dead or immune to the infection - and can play no further part in the epidemic.

Epidemics of this type are modelled mathematically by three families of non-

negative, integer valued random variables indexed by a continuous time parameter. The number of susceptibles is modelled by the process $\{S(t) : t \geq 0\}$, with $S(0)$ denoted by n. Since no individuals can enter the susceptible category during an epidemic, the number of susceptibles is non-increasing. The number of infectives is represented by the process $\{I(t) : t \geq 0\}$, and $I(0) = i$. Finally, the number of removed individuals is modelled by the process $\{R(t) : t \geq 0\}$ and without loss of generality, $R(0) = 0$. Since no individuals may leave the removed category once they have entered it, $R(t)$ is non-decreasing. Since the population is fixed, for all $t \geq 0$, $S(t) + I(t) + R(t) = n + i$.

Any pair of individuals make contact at the points of a Poisson process with rate $\frac{\beta}{n}$, and all of the $\binom{n+i}{2}$ Poisson processes are assumed to be independent. This implies that at time t, infections occur at a rate of $\frac{\beta}{n}S(t)I(t)$. The non-negative constant β encapsulates both the infectiousness of the disease and the susceptibility of the population, as a 'contact' is defined to be a meeting between two individuals sufficient to transfer the disease from an infective to a susceptible. Alternatively, contacts could be defined to occur at a rate $\frac{\beta'}{n+i}S(t)I(t)$. In this formulation when an infective makes a contact they choose an individual at random from the whole population to contact, whereas in our formulation contacts occur at $\frac{n}{n+i}$ times the rate, but contacts are chosen from only the initial susceptibles. This formulation is used as it highlights the connection with the branching process approximation: when $S(t) \approx S(0) = n$ then infections occur at rate $\beta I(t)$, as in the branching process.

At the instant of infection, the new infective is allocated an infectious period according to a non-negative random variable T_I. All instances of the random variable T_I are assumed to be independent of each other, and of the Poisson

processes governing the infections.

When the infectious period distribution T_I has an exponential distribution, the SIR epidemic model has been referred to as the General Stochastic Epidemic, and in this case the process $\{(S(t), I(t)) : t \geq 0\}$ has the Markov property.

The SIR epidemic model can be easily generalised to have multiple types of individual. Let K be the number of types of individual. For $t \geq 0$ let $\boldsymbol{S}(t) = (S_1(t), \ldots, S_K(t))$, where $S_k(t)$ represents the number of type k susceptible individuals at time t. Similarly let $I_k(t)$ and $R_k(t)$ denote the number of type k infective and removed individuals respectively at time t, and form the random vectors $\boldsymbol{I}(t) = (I_1(t), \ldots, I_K(t))$ and $\boldsymbol{R}(t) = (R_1(t), \ldots, R_K(t))$. A type k infective has infectious period distributed according to the random variable $T_{I,k}$ and makes contacts with a type j susceptible at the points of a Poisson process with rate $\beta_{k,j}/n_j$. Here $n_j = S_j(0)$ and the contact rates $\beta_{j,k}$ form the $K \times K$ matrix B. Again it is assumed that every pair of Poisson processes and infectious period distributions are independent. In this model no individual may change their type during the course of the epidemic, and if $K = 1$ this model reduces to the SIR epidemic model described above.

1.5.2 Branching process approximation

This section describes an approximation to the SIR epidemic model valid for large population sizes or during the early stages of the epidemic. First the approximating branching process is defined and then a coupling argument is set out to make clear the relationship between the two processes.

The term 'branching process' is used in several different ways in the literature,

however in this thesis it will be used exclusively to describe the continuous time branching process defined below. Branching processes in discrete time were first used by Galton and Watson (for a historical account see Mode, 1971) in order to model the survival of surnames, but they have come to have many other applications, particularly in biology (see Jagers, 1975).

At time zero, i initial ancestors begin their lifetimes. During its lifetime, each individual in the process independently gives birth to offspring at the points of a Poisson process with rate β, and these offspring start their own lifetimes immediately. Each lifetime has length distributed according to the random variable T_I, all instances of which are independent. Let $I(t)$ denote the number of individuals alive in the branching process at time t, so that overall, births occur at a rate $\beta I(t)$.

It is easy to understand that this branching process is an approximation to the epidemic process in the early stages or when n is large as in these circumstances $S(t) \approx S(0) = n$ and so infections will occur in the epidemic process at a rate approximately equal to $\beta I(t)$ and the infectious periods in the epidemic process have the same distribution as the lifetime distribution in the branching process. However, the relationship between the processes can be made much more precise by constructing them on the same probability space, so that there is a coupling between them. This allows us to pinpoint the precise instant at which the two processes first diverge, and to observe that after this instant the number of individuals alive in the branching process is an upper bound for the number of infectives in the epidemic process.

Coupling the branching process and the epidemic

Here a coupling between the epidemic process and the branching process, first used by Ball (1983), is constructed following Andersson and Britton (2000).

First, construct the branching process and then enlarge its probability space $(\Omega, \mathcal{F}, \mathrm{P})$ to include an infinite sequence (U_j), $j \geq 1$ of independent uniform random variables on $(0, 1)$. Next, construct the epidemic process from the branching process as follows. Label the n susceptibles in the epidemic process from $1, \ldots, n$ and associate each initial infective with an initial ancestor in the branching process. Let a contact occur in the epidemic process when a birth occurs in the branching process. The jth individual to be contacted is defined to be the initially susceptible individual with label $\lfloor nU_j \rfloor$, and if this individual is still susceptible then they become an infective. However, if they have already been contacted then the contact has been unsuccessful and the epidemic process does not change. The individual born in the branching process at this instant and all of their offspring are subsequently ignored in the construction of the epidemic process and are called 'ghosts'. When a death occurs in the branching process, the corresponding infective in the epidemic is removed.

By constructing the epidemic process from the branching process in this way it is clear that the number of infectives in the epidemic and the number of individuals in the branching process must coincide until the time of the first ghost, after which there must be more individuals (by the number of ghosts) in the branching process. Also note that in any time interval $(0, t]$, $t \in \mathbb{R}$, there can be only finitely many births and so the probability that the two processes coincide throughout $(0, t]$ tends to 1 as n tends to infinity.

1.5.3 Structured models

One of the least realistic assumptions made during the construction of the SIR epidemic is that the population is homogeneously mixing. This section briefly explores ways in which that assumption may be relaxed, in particular discussing two level mixing models, but first the random graph representation of an epidemic is briefly discussed.

Let each of the $n + i$ individuals in the epidemic correspond to a vertex in a graph. A directed edge between individuals j and k $(1 \leq j, k \leq n + i)$ exists if, given that individual j is infected, then they will go on to make an infectious contact with individual k during their infectious period. Thus, in the SIR epidemic model each edge from individual j will exist with probability $1 - \exp(-\beta T_{I,j}/n)$, where $T_{I,j}$ is the infectious period of individual j. Given the infectious periods $T_{I,j}$ $(1 \leq j \leq n + i)$ then all edges are assumed to exist independently. The total number of individuals to be infected by the epidemic is therefore the number of individuals connected by an unbroken (and directed) path leading from an initial infective. Clearly this graph representation of the epidemic loses any temporal information in the epidemic process, but it has the potential to allow a much more complicated social contact structure to be expressed. For more information about epidemics and graphs, see for example chapter 7 of Andersson and Britton (2000).

There are $2\binom{n+i}{2}$ possible directed edges on the graph of the epidemic and if each of these is to be modelled separately (possibly with dependence between them) then analysis of the model quickly becomes intractable. A more practical approach is to associate together groups of individuals that mix uniformly. The

maximum number of mixing groups an individual may belong to is called the number of levels of mixing of the model. Models with overlapping mixing groups and more than two levels of mixing are very difficult to make analytic progress with. However, if it is thought that more than two levels of mixing are required to realistically capture the mixing behaviour of the population, progress can be made using simulation studies, for example Longini *et al.* (2005), Ferguson *et al.* (2005) and Halloran *et al.* (2002).

Ball *et al.* (1997) define an epidemic model with two levels of mixing for a population partitioned into households. This model includes the models of Becker and Dietz (1995) and Becker *et al.* (2005) as special cases. Consider a population of N individuals divided into households. Since each individual belongs to precisely one household, the households form a partition of the population. Two types of infectious contact are possible - 'local contacts' between members of the same household and 'global contacts' between any two individuals in the population. Two individuals in the same household make local contacts at rate λ^L and any two individuals make global contacts at rate λ^G/N. Thus, if the population size N tends to infinity so that the household size distribution remains constant, this model tends to a multitype branching process in which an 'individual' in the branching process corresponds with a household in the epidemic process. For more details see Ball *et al.* (1997). This model is extended by Ball and Lyne (2001) to include multiple types of individuals.

1.5.4 Threshold parameters

A threshold parameter for an epidemic model gives an indication as to whether or not a large outbreak is possible. A reproduction number is a particular

threshold parameter that can be interpreted as the expected number of infectious individuals produced by a typical infectious individual in a completely susceptible population. For epidemic models with one level of mixing a simple formula for this reproduction number exists. For two level mixing models, several threshold parameters have been proposed.

Branching processes can exhibit two kinds of long-term behaviour: either the number of individuals follows an upward trend for all time or at some point the branching process dies out. A threshold parameter for the branching process indicates which of these two kinds of behaviour can occur. If the threshold parameter is less than one then the branching process will eventually become extinct and if it is larger than one there is a possibility that extinction will not occur. A branching process with threshold parameter equal to one will eventually become extinct, unless each individual produces precisely one offspring. A branching process with a threshold parameter strictly less than one is termed subcritical, and strictly greater than one supercritical. A critical branching process has a threshold parameter of precisely one. The reproduction number for the single type branching process is defined to be the expected number of offspring produced by an individual before their death. In a multitype branching process the reproduction number is calculated from the matrix of mean offspring M, in which $m_{i,j}$ is the mean number of type j individuals produced by a type i individual. If M is positive regular (i.e. there exists an $n \in \mathbb{N}$ such that every entry of M^n is strictly positive) then the reproduction number is the largest eigenvalue of M. The reproduction number for a branching process is a threshold parameter, and therefore it dictates the possible behaviour of the process. For more information about branching process threshold parameters

see for example Mode (1971) and Jagers (1975).

Epidemic models in large populations frequently exhibit two kinds of long-term behaviour: either the disease will die out in the early stages of the epidemic or there will be a large outbreak. Again, a threshold parameter dictates which of these two types of behaviour can occur. We have seen that the epidemic process is dominated by its branching process approximation, and the epidemic will die out before (or at the same instant as) the coupled branching process. Therefore a threshold parameter for the epidemic model is given by a threshold parameter for the approximating branching process. The basic reproduction number R_0 for a single type SIR epidemic model is defined to be the expected number of new infectives created by a typical infective in a totally susceptible population. For the one type SIR epidemic model, this means that $R_0 = \beta \mathrm{E}[T_I]$. A further advantage of the basic reproduction number is that it gives the critical vaccination coverage. For a perfect vaccine, the smallest proportion of the population needed to be vaccinated to ensure that a large outbreak occurs with probability zero is given by $1 - \frac{1}{R_0}$ when $R_0 > 1$. For more information about the basic reproduction number R_0 and its use in determining the critical vaccination coverage see for example Andersson and Britton (2000).

When two levels of mixing are introduced into the model, several different threshold parameters have been proposed. This thesis focuses only on the one proposed by Ball *et al.* (1997), given the symbol R_*, which is produced by interpreting the households in the epidemic model as 'individuals' in a branching process. R_* is defined to be the largest eigenvalue of the matrix of mean offspring M, where the offspring of infective i are those individuals globally contacted by i, plus any individuals globally contacted by the other members

of i's household, assuming that initially the population is infinitely large and entirely susceptible except for i. Let there be K types of individual living in a set $\mathcal{H}$ of possible household arrangements, where a household arrangement specifies the number of each type of individual. Ball and Lyne (2001) give the mean number of type j infectious offspring produced by a type i infective to be

$$m_{i,j} = \sum_{k=1}^{K} \sum_{\boldsymbol{h} \in \mathcal{H}} \alpha_i(\boldsymbol{h}) \mathrm{E}[N_{i,k}(\boldsymbol{h})] \mathrm{E}[T_{I,k}] \lambda_{k,j}^{G} \tag{1.1}$$

where $\alpha_i(\boldsymbol{h})$ is the proportion of type i infectives living in a household with arrangement $\boldsymbol{h}$, $N_{i,k}(\boldsymbol{h})$ is the number of type k individuals locally infected in a household of arrangement $\boldsymbol{h}$ in which one of the type i individuals is the sole initial infective (if $i = k$ this individual is included), $T_{I,k}$ is the infectious period distribution of a type k individual, and $\lambda_{k,j}^{G}$ is the rate at which a type k individual globally contacts a type j individual. The matrix M can be written as $M = N\Gamma\Lambda^{G}$, where N has entries $n_{i,k} = \sum_{\boldsymbol{h} \in \mathcal{H}} \alpha_i(\boldsymbol{h}) \mathrm{E}[N_{i,k}(\boldsymbol{h})]$, Γ is the diagonal matrix with entries $\gamma_{k,k} = \mathrm{E}[T_{I,k}]$ and Λ^{G} has entries $\lambda_{j,k}^{G}$.

Wald's identity for multitype epidemics (Ball, 1986) states that

$$\mathrm{E}[N_{i,k}(\boldsymbol{h})] \mathrm{E}[T_{I,k}] = \mathrm{E}[S_{i,k}(\boldsymbol{h})]$$

where $S_{i,k}(\boldsymbol{h})$ is the sum of all of the type k infectious periods in a household with arrangement $\boldsymbol{h}$ in which one of the type i individuals is the sole initial infective. Thus, equation (1.1) is equivalent to

$$m_{i,j} = \sum_{k=1}^{K} \sum_{\boldsymbol{h} \in \mathcal{H}} \alpha_i(\boldsymbol{h}) \mathrm{E}[S_{i,k}(\boldsymbol{h})] \lambda_{k,j}^{G}.$$

When all of the households are of size 1, there are no local infections and so the population is homogeneously mixing again. In this case, the threshold parameter R_* reduces to R_0. Since R_* generalises R_0 and applies to both epidemic and branching processes, all the threshold parameters will be denoted by R_* throughout the thesis, even if there is only a single level of mixing.

Becker *et al.* (2005) propose an alternative definition for the reproduction number of an epidemic model with two levels of mixing, which gives a reproduction number equal to R_*. They define the offspring of infective i to be the global contacts of i plus the individuals infected in the household subepidemics initiated by these global contacts. This leads to

$$\tilde{m}_{i,j} = \sum_{k=1}^{K} \sum_{\boldsymbol{h} \in \mathcal{H}} \mathrm{E}[T_{I,i}] \lambda_{i,k}^{G} \alpha_k(\boldsymbol{h}) \mathrm{E}[N_{k,j}(\boldsymbol{h})]$$

which implies that $\tilde{M} = \Gamma \Lambda^G N$. Equation (A.6.7) of Mardia *et al.* (1979) implies that for any non-singular $n \times n$ matrix C the eigenvalues of the $n \times n$ matrix A are equal to the eigenvalues of the matrix CAC^{-1}. If we take $C = N$ and $A = T\Lambda^G N$ we see that $\tilde{M}$ and M have the same eigenvalues, and therefore they must have the same threshold parameters.

Becker and Dietz (1995) suggest two further alternative definitions for the threshold parameter of an epidemic model on a population divided into households. In their model the disease is highly infectious, so if any household member contracts the disease, then every susceptible in the household is ultimately infected. There is a single type of infectious individual. Firstly, they derive a threshold parameter for the proliferation of infected individuals, called R_I. An individual is of type i (for $0 \leq i \leq N-1$, where N is the maximum household

size) if there are i susceptible individuals in their household just after they are infected. Under this definition of type, Becker and Dietz then define R_I to be the largest eigenvalue of the matrix of mean offspring M_I.

The second threshold parameter defined by Becker and Dietz (1995) relates to the proliferation of infected households. A household is said to be of type i ($1 \leq i \leq N$) if there are ultimately i individuals infected in that household, including the initial infective. This allows the matrix M_H to be defined, where $m^H_{i,j}$ is the mean number of infectious households of type j produced by a household of type i. R_H is defined to be the largest eigenvalue of the matrix M_H. Becker and Dietz state that

$$R_I = 1 \quad \Longleftrightarrow \quad R_H = 1,$$

although in general R_I is not equal to R_H. Calculating R_* for this model shows that in this case $R_* = R_H$.

In conclusion, R_* is the most general threshold parameter, as it reduces to R_0 and R_H in the circumstances in which the latter are defined. When R_I is defined, $R_I = 1$ if and only if $R_* = 1$ and so they give the same threshold.

Chapter 2

Asymptomatic carriers

2.1 Introduction

For many diseases it is possible for individuals to be infected and to infect others without any apparent symptoms or with just mild symptoms. Examples include influenza (Ferguson *et al.*, 2005), mumps (Conly and Johnston, 2007), rubella (Anderson and May, 1992) and polio (Lissauer and Claydon, 2001). These individuals are called asymptomatic carriers and can significantly increase the spread of the disease through a population whilst remaining unnoticed. This causes particular difficulties for emerging diseases, where the proportion of infected individuals that are asymptomatic carriers will be unknown. Clearly individuals without any obvious symptoms are difficult to identify and so estimates of the state of an epidemic must be drawn from observations of the symptomatic individuals alone. This chapter is concerned with calculating the probability that an epidemic has died out, given that no symptomatic individuals have been observed for a certain time.

Many human infectious diseases have asymptomatic infections, particularly viral diseases. Between a third and a half of influenza infections are asymptomatic, see for example modelling papers by Elveback *et al.* (1976), Longini *et al.* (2005) and Ferguson *et al.* (2005). These papers all include asymptomatic carriers as a type of infective that is 50% as infectious as symptomatic infectives, and in the first two papers carriers have different mixing behaviour and effective infectious periods to symptomatic infectives.

In mumps it is estimated that between 15% and 20% of infections are asymptomatic (Conly and Johnston, 2007). Rubella has between 20% and 50% of cases as asymptomatic (Anderson and May, 1992). In developed countries, half of the adult population show signs of having had cytomegalovirus, which is mild or sub-clinical in a normal host (Lissauer and Claydon, 2001). The majority of cases of Epstein-Barr virus (which can cause infectious mononucleosis, also known as glandular fever) are sub-clinical (Lissauer and Claydon, 2001). Finally, more than 90% of infections with the polio virus are asymptomatic (Lissauer and Claydon, 2001). It is clearly important to include asymptomatic infections in models for these diseases, but because asymptomatic infections are hard to detect, it can be very difficult to accurately estimate the proportion of infections that are caused by them.

In reality all the information about an epidemic is unlikely to be observed, in particular infection times and the beginnings of infectious periods are unlikely to be observed. Also, data may be concerned with specific geographical regions, a subset of the population (for example school children) and cases may go unreported. Infections will cluster together geographically because individuals living in close proximity are more likely to make infectious contacts. These

factors mean that it is difficult to extrapolate partial information about an epidemic to the whole population. Some work has been done on inference for partially observed epidemics, for example O'Neill and Roberts (1999), however although the process of infection is hidden, all of the removals are assumed to be observed.

When a new disease emerges there is a significant probability that it will die out in the very early stages, even if the reproduction number is greater than one. But if there are asymptomatic carriers of the disease, there may be a period in which no new cases are discovered but the disease is still present but unobserved within the population. Therefore, if a period without discoveries is observed, it is important to be able to quantify whether the epidemic has really died out, or if it still persists through asymptomatic carriage. In order to achieve this aim, the probability that the epidemic is over at time t given there have been no discoveries between time s and time t will be derived.

Glass *et al.* (2007) and Eichner and Dietz (1996) have different approaches to the problem of asymptomatic carriage. Glass *et al.* (2007) use Markov Chain Monte Carlo methods to calculate 95% bounds for the number of asymptomatic cases in the current generation of the infection, and make predictions concerning the number of diagnosed cases that will occur in the next generation of infection. They then test their methods on data from the SARS outbreak in 2003. Eichner and Dietz (1996) use a simulation model to estimate the length of time without observing a symptomatic case needed to be 95% certain that polio has been eradicated from a population of 200,000 individuals.

Many simulation papers include asymptomatic carriage in their models (see for example Elveback *et al.*, 1976; Halloran *et al.*, 2002; Ferguson *et al.*, 2005), but

the effect of the uncertainty surrounding the number of asymptomatic carriers on the results is rarely explored. The asymptomatic carriage model used in this chapter generalises one first proposed by Downton (1968), in which the infectious periods of symptomatic individuals have zero length.

2.1.1 Definition of the model

In order to model asymptomatic infections we consider a generalisation of the Markov SIR epidemic model (see section 1.5.1) with two infectious types. Consider a closed homogeneously mixing population of $n + i + c$ individuals, each of which can be in one of five categories at any time. Initially there are n susceptibles, i infectives, c carriers and no discovered or escaped individuals.

Individuals in the infective category make infectious contacts with each individual in the susceptible category at the points of a Poisson process with rate $(\beta_{1,1} + \beta_{1,2})/n$. Once contacted by an infective, a susceptible will become an infective with probability $\frac{\beta_{1,1}}{\beta_{1,1}+\beta_{1,2}}$ and a carrier otherwise. Infectives have infectious periods with length distributed according an exponential random variable with rate parameter γ, after which they enter the discovered category. It is at this instant that they are first thought to be observed. In the sequel, we shall assume that the number of discovered individuals is the only aspect of the epidemic that it is possible to observe.

Similarly, carriers have infectious periods of length Exp(μ) (i.e. exponential with mean μ^{-1}) and make infectious contacts with each susceptible at rate $(\beta_{2,1} + \beta_{2,2})/n$. Susceptibles contacted by carriers become infectives with probability $\frac{\beta_{2,1}}{\beta_{2,1}+\beta_{2,2}}$ and carriers otherwise. At the end of their infectious periods

carriers enter the escaped category. It is assumed that all instances of the infectious period distributions and the Poisson processes governing infectious contacts are mutually independent. Let the number of susceptible, infective, carrier, discovered and escaped individuals at time t be represented by the random variables $S(t)$, $I(t)$, $C(t)$, $D(t)$ and $E(t)$ respectively. Therefore, infectives are created at an overall rate of $(\beta_{1,1}I(t) + \beta_{2,1}C(t))S(t)/n$, carriers at a rate of $(\beta_{1,2}I(t) + \beta_{2,2}C(t))S(t)/n$ and the two types of removal (into the discovered and escaped categories respectively) occur at rates $\gamma I(t)$ and $\mu C(t)$.

At any time, the future behaviour of the epidemic process can be fully determined by the current numbers of susceptibles, infectives and carriers. For $t \geq 0$, let $\boldsymbol{S}(t) = (S(t), I(t), C(t))$ represent the state of the process at time t. In the sequel we will work only with this subprocess which will be referred to as the 'epidemic process'. Let $\boldsymbol{n} = (n, i, c)$ denote the initial state of the epidemic process and let $E_{\boldsymbol{n}} \subseteq \mathbb{Z}^3$ be the state space of the epidemic. A vector (x, y, z) is in $E_{\boldsymbol{n}}$ if the following inequalities are satisfied:

1. $0 \leq x \leq n$,
2. $y \geq 0$,
3. $z \geq 0$,
4. $x + y \leq n + i$,
5. $x + z \leq n + c$,
6. $x + y + z \leq n + i + c$.

It can be shown by induction (see Appendix A) that if $\boldsymbol{n}$ is not an absorbing

state $(i + c > 0)$ then

$$|E_{\boldsymbol{n}}| = (n+1)(i+1)(c+1) + \frac{n(n-1)(i+c+1)}{2} + \frac{n(n+1)(n+2)}{6}.$$

The threshold parameter R_* for this model is the largest eigenvalue of the mean offspring matrix

$$M = \begin{bmatrix} \frac{\beta_{1,1}}{\gamma} & \frac{\beta_{1,2}}{\gamma} \\ \frac{\beta_{2,1}}{\mu} & \frac{\beta_{2,2}}{\mu} \end{bmatrix},$$

so that

$$R_* = \frac{1}{2}\left(\frac{\beta_{1,1}}{\gamma} + \frac{\beta_{2,2}}{\mu} + \sqrt{\left(\frac{\beta_{1,1}}{\gamma} + \frac{\beta_{2,2}}{\mu}\right)^2 - \frac{4(\beta_{1,1}\beta_{2,2} - \beta_{1,2}\beta_{2,1})}{\gamma\mu}}\right).$$

For the special case in which newly infected individuals become infectives with probability π and carriers with probability $1-\pi$ independently of whether they were infected by an infective or a carrier, this simplifies to

$$R_* = \beta\left(\frac{\pi}{\gamma} + \frac{1-\pi}{\mu}\right),$$

as in this case $\beta_{1,1} = \beta_{2,1} = \pi\beta$ and $\beta_{1,2} = \beta_{2,2} = (1-\pi)\beta$.

2.1.2 Chapter structure

The aim of this chapter is to find the probability the epidemic is over given a period containing no new discoveries, i.e. $\mathrm{P}(I(t) + C(t) = 0 | D(s) = D(t))$. In order to solve this problem two methods are developed, firstly a path evaluation method (section 2.2) and then a matrix exponential method (section 2.3). In section 2.4 a branching process approximation to the epidemic process is con-

sidered. The effects of altering the parameters on the probability the epidemic is over at t given no discoveries in $(s, t]$ are explored for the epidemic and the branching process approximation in section 2.5. An extended model featuring independent households is considered in section 2.6. Finally in section 2.7, a related problem is considered, in which a stopping time T_t is defined as

$$T_t = \inf\{u \geq t : D(u) = D(u - t)\}.$$

The stopping time T_t represents the first time at which a time period of length t containing no discoveries has been observed. The probability the epidemic is over at time T_t is calculated.

2.2 Path evaluation method

The asymptomatic carriage epidemic model has the property that the process can visit no state twice. In fact the process is absorbed in at most $2n + i + c$ steps, since there can be at most n infections and $n + i + c$ removals. Since the state space is finite, the number of possible paths through the state space is therefore finite also. In this section, the temporal state probabilities are derived by conditioning on the path the epidemic process takes through the state space and solving the resulting differential equation. Kryscio (1975) used this method to find the temporal state probabilities of the General Stochastic Epidemic which was generalised for Downton's carrier borne epidemic model by Ball and Clancy (1995). Ball and Clancy also derive the generating function of the severity of the epidemic jointly with the transition probabilities, and the corresponding result is also derived here.

For $t \geq 0$, let $\boldsymbol{S}(t) = (S(t), I(t), C(t))$ be the state of the process at time t and let $\boldsymbol{n} = (n, i, c)$ denote the initial state of the process. Our interest focuses on the function

$$h_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{\theta}, t) = \mathrm{E}\left[e^{-\int_0^t \boldsymbol{\theta}.\boldsymbol{S}(u)\,\mathrm{d}u} \mathbb{1}_{\{\boldsymbol{S}(t)=\boldsymbol{x}\}} \middle| \boldsymbol{S}(0) = \boldsymbol{n}\right]$$

where $\boldsymbol{x} \in E_{\boldsymbol{n}}$ and $\boldsymbol{\theta} \in [0, \infty)^3$. For $\boldsymbol{u}, \boldsymbol{x} \in E_{\boldsymbol{n}}$, define a path d from $\boldsymbol{u}$ to $\boldsymbol{x}$ to be the ordered set of states $\{\boldsymbol{s}_0, \ldots, \boldsymbol{s}_L\} \subseteq E_{\boldsymbol{n}}$ such that

1. $\boldsymbol{s}_0 = \boldsymbol{u}$,
2. $\boldsymbol{s}_L = \boldsymbol{x}$,

3. For $j = 0, \ldots, L-1$,

$$\boldsymbol{s}_j - \boldsymbol{s}_{j-1} \in \{(-1,1,0),(-1,0,1),(0,-1,0),(0,0,-1)\},$$

4. $s_{j,2} + s_{j,3} > 0$ for $j = 0, \ldots, L-1$.

Conditions 1 to 4 imply that

5. $L = 2(u_1 - x_1) + u_2 - x_2 + u_3 - x_3$,

since there must be exactly $u_1 - x_1$ infections and $u_1 - x_1 + u_2 - x_2 + u_3 - x_3$ removals. Let $D(\boldsymbol{u}, \boldsymbol{x})$ denote the (possibly empty) set of all paths from $\boldsymbol{u}$ to $\boldsymbol{x}$, and let v_d denote the probability that the process takes path d. By the law of total probability,

$$h_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{\theta}, t) = \sum_{d \in D(\boldsymbol{n}, \boldsymbol{x})} h(\boldsymbol{x}, \boldsymbol{\theta}, t|d) v_d,$$

where $h(\boldsymbol{x}, \boldsymbol{\theta}, t|d)$ denotes $h_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{\theta}, t)$ conditional on taking path d.

To find v_d, the probability that the process takes path d, note that

$$\text{P(The process jumps from } \boldsymbol{s}_j \text{ to } \boldsymbol{s}_{j+1}) \;=\; \frac{a_j}{b_j}$$

where a_j is the rate at which the process goes from state $\boldsymbol{s}_j$ to $\boldsymbol{s}_{j+1}$, and b_j is the total rate at which the process leaves state $\boldsymbol{s}_j$. Thus,

$$a_j \;=\; \begin{cases} (\beta_{1,1} s_{j,2} + \beta_{2,1} s_{j,3}) s_{j,1}/n & s_{j+1,2} = s_{j,2} + 1, \\ (\beta_{1,2} s_{j,2} + \beta_{2,2} s_{j,3}) s_{j,1}/n & s_{j+1,3} = s_{j,3} + 1, \\ \gamma s_{j,2} & s_{j+1,2} = s_{j,2} - 1, \\ \mu s_{j,3} & s_{j+1,3} = s_{j,3} - 1, \end{cases} \tag{2.1}$$

$$b_j = (\beta_{1,1}s_{j,2} + \beta_{2,1}s_{j,3})s_{j,1}/n + (\beta_{1,2}s_{j,2} + \beta_{2,2}s_{j,3})s_{j,1}/n + \gamma s_{j,2} + \mu s_{j,3}. \tag{2.2}$$

Thus,

$$v_d = \prod_{j=0}^{L-1} \frac{a_j}{b_j}.$$

Using the Markov property over an infinitesimal interval it is possible to derive and solve a set of differential equations for $h(\boldsymbol{s}_j, \boldsymbol{\theta}, t|d)$ for $j = 0, \ldots, L$, as follows. To simplify the notation, write $w_j(t)$ for $h(\boldsymbol{s}_j, \boldsymbol{\theta}, t|d)$ and let $\mathcal{F}(t)$ denote the sigma field generated by the process up to time $t \geq 0$. Then

$$\begin{aligned}
w_j(t+\Delta t) &= \mathrm{E}\left[\exp\left\{-\int_0^{t+\Delta t} \boldsymbol{\theta}.\boldsymbol{S}(u)\,\mathrm{d}u\right\} \mathbb{1}_{\{\boldsymbol{S}(t+\Delta t)=\boldsymbol{s}_j\}}\middle| d\right] \\
&= \mathrm{E}\left[\mathrm{E}\left[\exp\left\{-\int_0^{t+\Delta t} \boldsymbol{\theta}.\boldsymbol{S}(u)\,\mathrm{d}u\right\} \mathbb{1}_{\{\boldsymbol{S}(t+\Delta t)=\boldsymbol{s}_j\}}\middle| \mathcal{F}(t), d\right]\middle| d\right] \\
&= \mathrm{E}\left[\exp\left\{-\int_0^{t} \boldsymbol{\theta}.\boldsymbol{S}(u)\,\mathrm{d}u\right\}\right. \\
&\quad \left.\times \mathrm{E}\left[\exp\left\{-\int_t^{t+\Delta t} \boldsymbol{\theta}.\boldsymbol{S}(u)\,\mathrm{d}u\right\} \mathbb{1}_{\{\boldsymbol{S}(t+\Delta t)=\boldsymbol{s}_j\}}\middle| \mathcal{F}(t), d\right]\middle| d\right].
\end{aligned}$$

However,

$$\exp\left\{-\int_t^{t+\Delta t} \boldsymbol{\theta}.\boldsymbol{S}(u)\,\mathrm{d}u\right\} = 1 - \Delta t\boldsymbol{\theta}.\boldsymbol{S}(t) + o(\Delta t),$$

and so,

$$\begin{aligned}
&w_j(t+\Delta t) \\
&= \mathrm{E}\left[\exp\left\{-\int_0^{t} \boldsymbol{\theta}.\boldsymbol{S}(u)\,\mathrm{d}u\right\}(1-\Delta t\boldsymbol{\theta}.\boldsymbol{S}(t))\mathrm{E}\left[\mathbb{1}_{\{\boldsymbol{S}(t+\Delta t)=\boldsymbol{s}_j\}}\middle| \mathcal{F}(t), d\right]\middle| d\right] + o(\Delta t).
\end{aligned}$$

Next consider the indicator function $\mathbb{1}_{\{\boldsymbol{S}(t+\Delta t)=\boldsymbol{s}_j\}}$. This function is one if and

only if one of the following events occur.

1. $\boldsymbol{S}(t) = \boldsymbol{s}_j$ and no events occur in $(t, t + \Delta t]$,
2. $\boldsymbol{S}(t) = \boldsymbol{s}_{j-1}$ and one event occurs in $(t, t + \Delta t]$,
3. $\boldsymbol{S}(t) = \boldsymbol{s}_{j-k}$ for $1 < k \leq j$ and k events occur in $(t, t + \Delta t]$.

Given $\boldsymbol{S}(t) = \boldsymbol{s}_j$, the first of these events occurs with probability $1-\Delta t b_j+o(\Delta t)$. Given $\boldsymbol{S}(t) = \boldsymbol{s}_{j-1}$, the second event occurs with probability $\Delta t b_{j-1} + o(\Delta t)$. The third event occurs with probability $o(\Delta t)$. Thus,

$$\mathrm{E}\left[\mathbb{1}_{\{\boldsymbol{S}(t+\Delta t)=\boldsymbol{s}_j\}}\middle|\mathcal{F}(t), d\right] = \mathbb{1}_{\{\boldsymbol{S}(t)=\boldsymbol{s}_j\}}(1 - \Delta t b_j) + \mathbb{1}_{\{\boldsymbol{S}(t)=\boldsymbol{s}_{j-1}\}}\Delta t b_{j-1} + o(\Delta t).$$

Thus,

$$\begin{aligned} w_j(t + \Delta t) &= (1 - \Delta t(\boldsymbol{\theta}.\boldsymbol{S}(t) + b_j))\mathrm{E}\left[\exp\left\{-\int_0^t \boldsymbol{\theta}.\boldsymbol{S}(u)\,\mathrm{d}u\right\}\mathbb{1}_{\{\boldsymbol{S}(t)=\boldsymbol{s}_j\}}\middle|d\right] \\ &\quad +\Delta t b_{j-1}\mathrm{E}\left[\exp\left\{-\int_0^t \boldsymbol{\theta}.\boldsymbol{S}(u)\,\mathrm{d}u\right\}\mathbb{1}_{\{\boldsymbol{S}(t)=\boldsymbol{s}_{j-1}\}}\middle|d\right] + o(\Delta t) \\ &= (1 - \Delta t(\boldsymbol{\theta}.\boldsymbol{S}(t) + b_j))w_j(t) + \Delta t b_{j-1} w_{j-1}(t) + o(\Delta t), \end{aligned}$$

which upon rearrangement and taking the limit $\Delta t \to 0$ yields that for $j = 0, \ldots, L$,

$$\frac{\mathrm{d}w_j(t)}{\mathrm{d}t} = -w_j(t)(\boldsymbol{\theta}.\boldsymbol{S}(t) + b_j) + w_{j-1}(t)b_{j-1}.$$

This implies that the $(L + 1)$-vector

$$\boldsymbol{w}(t) = \begin{bmatrix} w_0(t) \\ \vdots \\ w_L(t) \end{bmatrix}$$

satisfies the differential equation

$$\frac{\mathrm{d}\boldsymbol{w}(t)}{\mathrm{d}t} = A\boldsymbol{w}(t) \tag{2.3}$$

where the $(L+1)\times(L+1)$ matrix A is defined to be

$$A = \begin{bmatrix} -\boldsymbol{\theta}.\boldsymbol{s}_0 - b_0 & 0 & \cdots & 0 \\ b_0 & -\boldsymbol{\theta}.\boldsymbol{s}_1 - b_1 & \cdots & 0 \\ 0 & b_1 & \cdots & 0 \\ & & & \\ \vdots & & \ddots & \vdots \\ & & & \\ 0 & \cdots & b_{L-1} & -\boldsymbol{\theta}.\boldsymbol{s}_L - b_L \end{bmatrix}.$$

The initial conditions for equation (2.3) are given by

$$\boldsymbol{w}(0) = [1\ 0\ 0\ \ldots\ 0]^T_{L+1}$$

where $[\cdot]_l$ denotes a vector of length l. Theorem 1 of Severo (1969) gives a complete solution to differential difference equations of this type. By applying this result we find that for $t \geq 0$,

$$\boldsymbol{w}(t) = C\boldsymbol{e}(t)$$

where for $t \geq 0$,

$$\boldsymbol{e}(t) = \begin{bmatrix} \exp(-t(\boldsymbol{\theta}.\boldsymbol{s}_0 + b_0)) \\ \exp(-t(\boldsymbol{\theta}.\boldsymbol{s}_1 + b_1)) \\ \vdots \\ \exp(-t(\boldsymbol{\theta}.\boldsymbol{s}_L + b_L)) \end{bmatrix}_{L+1}$$

and the $(L+1)\times(L+1)$ matrix C has elements $c_{u,v}$ specified by

$$c_{u,v} = \begin{cases} 0 & 1 \le u < v, \\ 1 & 1 = u = v, \\ \boldsymbol{a}(u,u-1)^T C(u-1,v)\boldsymbol{h}(v,u) & 1 \le v < u, \\ -\sum_{k=1}^{u-1} c_0(u,k) & 1 < u = v. \end{cases} \tag{2.4}$$

The vector $\boldsymbol{a}(u,v)$ comprises the first v elements of the uth row of the matrix A (for $1 \le v < u \le L+1$), so that

$$\boldsymbol{a}(u,v) = \begin{cases} [0\ 0\ \ldots\ 0]_v & 1 \le v < u-1, \\ [0\ 0\ \ldots\ b_{u-2}]_v & v = u-1. \end{cases}$$

The symbol $\boldsymbol{h}(v,u)$ is the $(u-v)$-vector defined by

$$\boldsymbol{h}(v,u) = \begin{bmatrix} \delta_0(\boldsymbol{\theta}.\boldsymbol{s}_{u-1} + b_{u-1} - \boldsymbol{\theta}.\boldsymbol{s}_{v-1} - b_{v-1}) \\ \delta_1(\boldsymbol{\theta}.\boldsymbol{s}_{u-1} + b_{u-1} - \boldsymbol{\theta}.\boldsymbol{s}_{v-1} - b_{v-1}) \\ \vdots \\ \delta_{u-v-1}(\boldsymbol{\theta}.\boldsymbol{s}_{u-1} + b_{u-1} - \boldsymbol{\theta}.\boldsymbol{s}_{v-1} - b_{v-1}) \end{bmatrix}_{u-v}$$

where for $y \in \mathbb{R}$ and $k = 0, 1, \ldots,$

$$\delta_k(y) = \begin{cases} \frac{k!}{y^{k+1}} \sum_{j=0}^{k} \frac{(-1)^{k-j}(yt)^k}{j!} & y \ne 0, \\ \frac{t^{k+1}}{k+1} & y = 0. \end{cases}$$

For $u > v$, the matrices $C(u,v)$ in equation (2.4) are of dimension $u \times (u-v)$ and have (r,s)th element equal to

$$C(u,v)\Big|_{r,s} = \begin{cases} c_{s-1}(r,v) & r \ge v+s-1, \\ 0 & \text{otherwise.} \end{cases}$$

Finally, for $u > v$ the functions $c_j(u, v)$ $(j = 0, \ldots, u - v)$ can be found recursively from the relation

$$c_{u,v} = c_0(u, v) + c_1(u, v)t + \ldots + c_{u-v}(u, v)t^{u-v} \tag{2.5}$$

if it is further assumed that the functions $c_j(u, v)$ are independent of t. If the eigenvalues of A given by $\{\boldsymbol{\theta}.\boldsymbol{s}_j + b_j : j = 0, \ldots, L\}$ are distinct, then a relatively simple solution exists, as the matrix C is independent of t. If the eigenvalues of A are not distinct, the parameters γ, μ and $\beta_{u,v}$ $(u, v \in \{1, 2\})$ can be altered infinitesimally so that the eigenvalues become distinct and the value of R_* is unchanged. From here onwards, it will be assumed that the eigenvalues of A are indeed distinct, and therefore the vector $\boldsymbol{h}(v, u)$ has no entries of the form $\delta_j(0)$ for $j = 0, \ldots, u - v - 1$.

Substituting (2.4) into (2.5) for the case in which $u > v$ yields,

$$\sum_{l=0}^{u-v} c_l(u, v)t^l = \sum_{l=1}^{u-v} b_{j-2}c_{l-1}(u - 1, v)\delta_{l-1}(\boldsymbol{\theta}.\boldsymbol{s}_{u-1} + b_{u-1} - \boldsymbol{\theta}.\boldsymbol{s}_{v-1} - b_{v-1}). \tag{2.6}$$

Notice that if $y \neq 0$ then $\delta_l(y)$ contains powers of t up to l. Thus, for $u > v$, equating coefficients of t^{u-v} in (2.6) gives

$$c_{u-v}(u, v) = 0.$$

If $u - v > 1$, then this can be re-written $c_{u-v-1}(u - 1, v) = 0$. Equating

coefficients of t^{u-v-1} in equation (2.6) therefore gives

$$c_{u-v-1}(u,v) = 0.$$

Iterating this argument shows that the constants of the form $c_j(u,v)$ with index $j \in \{u-v, u-v-1, \ldots, 1\}$ are all zero. All the non-zero constants are therefore of the form $c_0(u,v)$. Equation (2.5) then gives $c_{u,v} = c_0(u,v)$. This implies that the matrix C can be written

$$c_{u,v} = \begin{cases} 0 & 1 \leq u < v, \\ 1 & 1 = u = v, \\ \frac{b_{u-2} c_{u-1,v}}{\boldsymbol{\theta}.\boldsymbol{s}_{u-1} + b_{u-1} - \boldsymbol{\theta}.\boldsymbol{s}_{v-1} - b_{v-1}} & 1 \leq v < u, \\ -\sum_{k=1}^{u-1} c_{u,k} & 1 < u = v. \end{cases} \tag{2.7}$$

This recursive relation allows a formula for $c_{u,v}$ to be derived, but first a lemma is needed.

Lemma 2.1 *For any distinct real numbers $x_1, \ldots, x_n$ ($n > 1$),*

$$\sum_{j=1}^{n} \prod_{\substack{k=1 \\ k \neq j}}^{n} \frac{1}{x_j - x_k} = 0.$$

This lemma is proved in Appendix B. We are now ready to prove that for $1 \leq u, v \leq L+1$,

$$c_{u,v} = \begin{cases} \left(\prod_{k=0}^{u-2} b_k \right) \prod_{\substack{k=1 \\ k \neq v}}^{u} (\boldsymbol{\theta}.\boldsymbol{s}_{k-1} + b_{k-1} - \boldsymbol{\theta}.\boldsymbol{s}_{v-1} - b_{v-1})^{-1} & v \leq u, \\ 0 & v > u, \end{cases} \tag{2.8}$$

by induction on u.

Equation (2.7) shows that the base case $u = 1$ holds, assuming that the empty product is unity. Next, assume the inductive hypothesis - that equation (2.8) holds for all $u < u^*$ and for all v. Firstly, note that if $v > u^*$ then equation (2.7) implies that $c_{u^*,v} = 0$. Next treat the case $v < u^*$. From equation (2.7),

$$\begin{aligned} c_{u^*,v} &= \frac{b_{u^*-2}}{\boldsymbol{\theta}.\boldsymbol{s}_{u^*-1} + b_{u^*-1} - \boldsymbol{\theta}.\boldsymbol{s}_{v-1} - b_{v-1}} \\ &\quad \times \left(\prod_{k=0}^{u^*-3} b_k\right) \prod_{\substack{k=1 \\ k \neq v}}^{u^*-1} (\boldsymbol{\theta}.\boldsymbol{s}_{k-1} + b_{k-1} - \boldsymbol{\theta}.\boldsymbol{s}_{v-1} - b_{v-1})^{-1} \\ &= \left(\prod_{k=0}^{u^*-2} b_k\right) \prod_{\substack{k=1 \\ k \neq v}}^{u^*} (\boldsymbol{\theta}.\boldsymbol{s}_{k-1} + b_{k-1} - \boldsymbol{\theta}.\boldsymbol{s}_{v-1} - b_{v-1})^{-1} \end{aligned}$$

as required. The only remaining case is $v = u^*$. From equation (2.7),

$$\begin{aligned} c_{u^*,u^*} &= -\sum_{j=1}^{u^*-1} c_{u^*,j} \\ &= -\sum_{j=1}^{u^*-1} \left(\prod_{k=0}^{u^*-2} b_k\right) \prod_{\substack{l=1 \\ l \neq j}}^{u^*} (\boldsymbol{\theta}.\boldsymbol{s}_{l-1} + b_{l-1} - \boldsymbol{\theta}.\boldsymbol{s}_{j-1} - b_{j-1})^{-1} \\ &= \left(\prod_{k=0}^{u^*-2} b_k\right) \prod_{\substack{l=1 \\ l \neq u^*}}^{u^*} (\boldsymbol{\theta}.\boldsymbol{s}_{l-1} + b_{l-1} - \boldsymbol{\theta}.\boldsymbol{s}_{u^*-1} - b_{u^*-1})^{-1} \end{aligned}$$

by Lemma 2.1. This completes the proof of (2.8).

Now, the following lemma can be proved.

Lemma 2.2 *If the real numbers* $\{\boldsymbol{\theta}.\boldsymbol{s}_j + b_j : j = 0, \ldots, L\}$ *are distinct, then for* $\boldsymbol{x} \in E_{\boldsymbol{n}}$, $\boldsymbol{\theta} \in [0, \infty)^3$ *and* $t \in [0, \infty)$,

$$h_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{\theta}, t) = \sum_{\boldsymbol{u} \in E_{\boldsymbol{n}}(\boldsymbol{x})} C_1(\boldsymbol{n} \to \boldsymbol{u}) C_2(\boldsymbol{u} \to \boldsymbol{x}) \exp(-t\lambda(\boldsymbol{u}, \boldsymbol{\theta}))$$

where $E_{\boldsymbol{n}}(\boldsymbol{x}) = \{\boldsymbol{u} \in E_{\boldsymbol{n}} : \boldsymbol{x} \in E_{\boldsymbol{u}}\}$,

$$\lambda(\boldsymbol{u}, \boldsymbol{\theta}) = ((\beta_{1,1} + \beta_{1,2})u_2 + (\beta_{2,1} + \beta_{2,2})u_3)\frac{u_1}{n} + u_1\theta_1 + u_2(\theta_2 + \gamma) + u_3(\theta_3 + \mu)$$

and

$$\begin{aligned} C_1(\boldsymbol{n} \to \boldsymbol{u}) &= \sum_{d \in D_1} \prod_{k=0}^{L_1 - 1} \frac{a_k}{\boldsymbol{\theta}.\boldsymbol{s}_k + b_k - \boldsymbol{\theta}.\boldsymbol{s}_{L_1} - b_{L_1}}, \\ C_2(\boldsymbol{u} \to \boldsymbol{x}) &= \sum_{d \in D_2} \prod_{k=0}^{L_2 - 1} \frac{a_k}{\boldsymbol{\theta}.\boldsymbol{s}_{k+1} + b_{k+1} - \boldsymbol{\theta}.\boldsymbol{s}_0 - b_0}. \end{aligned}$$

Here D_1 *is the set of paths from* $\boldsymbol{n}$ *to* $\boldsymbol{u}$, D_2 *is the set of paths from* $\boldsymbol{u}$ *to* $\boldsymbol{x}$, *and for* $j \in \{1, 2\}$, L_j *is the length of all the paths in* D_j.

Proof:

Recall that

$$\begin{aligned} h_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{\theta}, t) &= \sum_{d \in D(\boldsymbol{n}, \boldsymbol{x})} v_d h(\boldsymbol{x}, \boldsymbol{\theta}, t|d) \\ &= \sum_{d \in D(\boldsymbol{n}, \boldsymbol{x})} v_d w_L(t) \\ &= \sum_{d \in D(\boldsymbol{n}, \boldsymbol{x})} \left(\prod_{k=0}^{L-1} \frac{a_k}{b_k} \right) \sum_{j=0}^{L} c_{L+1, j+1} \exp(-t(\boldsymbol{\theta}.\boldsymbol{s}_j + b_j)) \end{aligned}$$

$$= \sum_{d \in D(\boldsymbol{n},\boldsymbol{x})} \sum_{j=0}^{L} \left(\prod_{k=0}^{L-1} a_k \right) \exp(-t(\boldsymbol{\theta}.\boldsymbol{s}_j + b_j)) \times \prod_{\substack{l=1 \\ l \neq j}}^{j} (\boldsymbol{\theta}.\boldsymbol{s}_{l-1} + b_{l-1} - \boldsymbol{\theta}.\boldsymbol{s}_{u^*-1} - b_{u^*-1})^{-1}.$$

This result can be re-arranged as follows. Let $D(\boldsymbol{n}, \boldsymbol{u}, \boldsymbol{x})$ be the set of paths from $\boldsymbol{n}$ to $\boldsymbol{x}$ passing through $\boldsymbol{u}$. Let L_1 be the length of the path from $\boldsymbol{n}$ to $\boldsymbol{u}$ and let L_2 be the length of the path from $\boldsymbol{u}$ to $\boldsymbol{x}$, so that $L = L_1 + L_2$. Let D_1 be the set of paths from $\boldsymbol{n}$ to $\boldsymbol{u}$ and D_2 be the set of paths from $\boldsymbol{u}$ to $\boldsymbol{x}$, so that $D(\boldsymbol{n}, \boldsymbol{u}, \boldsymbol{x}) = D_1 \times D_2$. Finally define $E_{\boldsymbol{n}}(\boldsymbol{x}) \subseteq E_{\boldsymbol{n}}$ such that $\boldsymbol{u} \in E_{\boldsymbol{n}}(\boldsymbol{x})$ if and only if $\boldsymbol{x} \in E_{\boldsymbol{u}}$. In other words, $E_{\boldsymbol{n}}(\boldsymbol{x})$ is the subset of the state space that can be connected by a path to $\boldsymbol{x}$.

Now, collect together coefficients of the same exponential term, taking $L_1 = j$ so that $\boldsymbol{u} = \boldsymbol{s}_j$. Thus,

$$\begin{aligned} h_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{\theta}, t) &= \sum_{\boldsymbol{u} \in E_{\boldsymbol{n}}(\boldsymbol{x})} \sum_{d \in D(\boldsymbol{n},\boldsymbol{u},\boldsymbol{x})} \left(\prod_{k=0}^{L-1} a_k \right) \exp(-t\lambda(\boldsymbol{u}, \boldsymbol{\theta})) \\ &\qquad \times \prod_{\substack{l=0 \\ l \neq L_1}}^{L} (\boldsymbol{\theta}.\boldsymbol{s}_l + b_l - \boldsymbol{\theta}.\boldsymbol{s}_{L_1} - b_{L_1})^{-1} \\ &= \sum_{\boldsymbol{u} \in E_{\boldsymbol{n}}(\boldsymbol{x})} C_1(\boldsymbol{n} \to \boldsymbol{u}) C_2(\boldsymbol{u} \to \boldsymbol{x}) \exp(-t\lambda(\boldsymbol{u}, \boldsymbol{\theta})) \end{aligned}$$

where

$$\lambda(\boldsymbol{u}, \boldsymbol{\theta}) = ((\beta_{1,1} + \beta_{1,2})u_2 + (\beta_{2,1} + \beta_{2,2})u_3)\frac{u_1}{n} + u_1\theta_1 + u_2(\theta_2 + \gamma) + u_3(\theta_3 + \mu),$$

and

$$C_1(\boldsymbol{n} \to \boldsymbol{u}) = \sum_{d \in D_1} \prod_{k=0}^{L_1-1} \frac{a_k}{\boldsymbol{\theta}.\boldsymbol{s}_k + b_k - \boldsymbol{\theta}.\boldsymbol{s}_{L_1} - b_{L_1}},$$
$$C_2(\boldsymbol{u} \to \boldsymbol{x}) = \sum_{d \in D_2} \prod_{k=0}^{L_2-1} \frac{a_k}{\boldsymbol{\theta}.\boldsymbol{s}_{k+1} + b_{k+1} - \boldsymbol{\theta}.\boldsymbol{s}_0 - b_0}.$$

This completes the proof of Lemma 2.2.

2.2.1 Application

This section describes how the function $h_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{\theta}, t)$ can be used to calculate properties of interest.

1. The state probabilities.

$$\mathrm{P}(\boldsymbol{S}(t) = \boldsymbol{x} | \boldsymbol{S}(0) = \boldsymbol{n}) = h_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{0}, t)$$

2. The probability of no discoveries in $(0, t]$.

$$\begin{aligned} \mathrm{P}(D(0) = D(t)) &= \sum_{\boldsymbol{x} \in E_{\boldsymbol{n}}} \mathrm{P}(D(0) = D(t) \text{ and } \boldsymbol{S}(t) = \boldsymbol{x}) \\ &= \sum_{\boldsymbol{x} \in E_{\boldsymbol{n}}} \sum_{d \in D'(\boldsymbol{n}, \boldsymbol{x})} h(\boldsymbol{x}, \boldsymbol{0}, t|d) \end{aligned}$$

where $D'(\boldsymbol{n}, \boldsymbol{x}) \subseteq D(\boldsymbol{n}, \boldsymbol{x})$ is the set of paths from $\boldsymbol{n}$ to $\boldsymbol{x}$ that contain no discoveries. Obviously if $x_2 < i$ the set $D'(\boldsymbol{n}, \boldsymbol{x})$ will be empty.

3. The probability of no discoveries in $(s, t]$.

$$\begin{aligned} \mathrm{P}(D(s) = D(t)) &= \sum_{\boldsymbol{u} \in E_{\boldsymbol{n}}} \mathrm{P}(D(s) = D(t) | \boldsymbol{S}(s) = \boldsymbol{u}) \mathrm{P}(\boldsymbol{S}(s) = \boldsymbol{u}) \\ &= \sum_{\boldsymbol{u} \in E_{\boldsymbol{n}}} \mathrm{P}(D(0) = D(t-s) | \boldsymbol{S}(0) = \boldsymbol{u}) \mathrm{P}(\boldsymbol{S}(s) = \boldsymbol{u}) \end{aligned}$$

4. The probability there are k infectious individuals at time t, given no discoveries in $(s, t]$.

$$\mathrm{P}(I(t) + C(t) = k | D(s) = D(t)) = \frac{\mathrm{P}(I(t) + C(t) = k \text{ and } D(s) = D(t))}{\mathrm{P}(D(s) = D(t))}$$

where

$$\begin{aligned} &\mathrm{P}(I(t) + C(t) = k \text{ and } D(s) = D(t)) \\ &= \sum_{\substack{\boldsymbol{u} \in E_{\boldsymbol{n}} \\ u_2 + u_3 = k}} \mathrm{P}(I(t-s) + C(t-s) = k \text{ and } D(0) = D(t-s) | \boldsymbol{S}(0) = \boldsymbol{u}) \\ &\qquad \times \mathrm{P}(\boldsymbol{S}(s) = \boldsymbol{u}) \\ &= \sum_{\substack{\boldsymbol{u} \in E_{\boldsymbol{n}} \\ u_2 + u_3 = k}} h'_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{0}, t-s) \mathrm{P}(\boldsymbol{S}(s) = \boldsymbol{u}) \end{aligned}$$

and where $h'_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{\theta}, t) = \sum_{d \in D'(\boldsymbol{u}, \boldsymbol{x})} h(\boldsymbol{x}, \boldsymbol{\theta}, t) v_d$.

5. The expected severity of the epidemic.

$$\mathrm{E}\left[\int_0^\infty I(u) + C(u) \, \mathrm{d}u\right] = \sum_{x=0}^{n} \left[\frac{\partial}{\partial \theta_2} h_{\boldsymbol{n}}([x\,0\,0], \boldsymbol{\theta}, \infty) + \frac{\partial}{\partial \theta_3} h_{\boldsymbol{n}}([x\,0\,0], \boldsymbol{\theta}, \infty)\right]_{\boldsymbol{\theta} = \boldsymbol{0}}$$

The usefulness and flexibility of these functions is quickly apparent, however they are very intensive to compute for even moderate population sizes. The size

of the state space is given by a polynomial in n with degree three, and therefore the number of possible paths increases with even more rapidity. When $n = 8$, a program written in C takes about 20 minutes to complete, and increasing n by one causes approximately a tenfold increase in computation time. As n is increased above eight, for some parameter choices truncation errors begin to effect the results. Numerical progress is therefore difficult to make for values of n greater than ten.

2.3 Matrix exponential method

Although very flexible, the path evaluation method is computationally intensive. However, it is also possible to calculate the probability the epidemic is over at time t given no discoveries in $(s, t]$ by utilising matrix exponentials.

The asymptomatic carriage epidemic model is a continuous time Markov process on a finite state space, and so the state probabilities at time t can be found by taking the matrix exponential of the product of the generator matrix Q and t. This idea can be extended to calculate the probability of no discoveries in $(0, t]$. First a new matrix R is defined to be the matrix Q with the off-diagonal entries that represent discovery transitions set to zero. Define a family of $|E_{\boldsymbol{n}}| \times |E_{\boldsymbol{n}}|$ matrices $R(t)$ with (u, v)th entry $r_{u,v}(t)$ representing the probability the epidemic is in state v at time t and there were no discoveries in $(0, t]$, given that the process was initially in state u. First we will show that $R(\Delta t) = \Delta t R + I + o(\Delta t)$, where I is the $|E_{\boldsymbol{n}}| \times |E_{\boldsymbol{n}}|$ identity matrix, and then by deriving the forward equations for $R(t)$ we will see that $R(t) = \exp(Rt)$.

First, note that for $u, v \in E_{\boldsymbol{n}}$ with $u \neq v$,

$$\begin{aligned} r_{u,v}(\Delta t) &= \text{P(jump from } u \text{ to } v \text{ in } (0, \Delta t] \text{ and } D(0) = D(\Delta t)) \\ &\quad + \text{P(more than one jump in } (0, \Delta t] \text{ and } D(0) = D(\Delta t)) \\ &= r_{u,v}\Delta t + o(\Delta t) \\ r_{v,v}(\Delta t) &= \text{P(no jumps in } (0, \Delta t]) \\ &\quad + \text{P(more than one jump in } (0, \Delta t] \text{ and } D(0) = D(\Delta t)) \\ &= 1 + r_{v,v}\Delta t + o(\Delta t) \end{aligned}$$

and so $R(\Delta t) = \Delta t R + I + o(\Delta t)$. Analogously to the generator matrix Q, we have that

$$R = \lim_{t \to 0} \frac{R(t) - I}{t}.$$

Next, we calculate the matrix $R(t)$ from the forward equations. Note that for $u, v \in E_{\boldsymbol{n}}$

$$\begin{aligned} r_{u,v}(t + \Delta t) &= r_{u,v}(t) r_{v,v}(\Delta t) + \sum_{w \neq v} r_{u,w}(t) r_{w,v}(\Delta t) + o(\Delta t) \\ &= r_{u,v}(t)(1 + r_{v,v}\Delta t) + \sum_{w \neq v} r_{u,w}(t) r_{w,v} \Delta t + o(\Delta t) \\ &= r_{u,v}(t) + \Delta t \sum_{w} r_{u,w}(t) r_{w,v} + o(\Delta t) \end{aligned}$$

taking the limit $\Delta t \to 0$ implies that

$$\frac{\mathrm{d}}{\mathrm{d}t} r_{u,v}(t) = [R(t)R]_{u,v}$$

and so

$$\frac{\mathrm{d}}{\mathrm{d}t} R(t) = R(t)R$$

with the boundary condition

$$R(0) = I.$$

This differential equation has the unique solution

$$R(t) = \exp(Rt).$$

Let $\boldsymbol{\pi}$ be a row vector representing the initial distribution of the process and let $\mathbf{1}$ be a column vector of ones. By conditioning on the state of the process

at time s, we see that

$$\mathrm{P}(D(s) = D(t)) = \boldsymbol{\pi} \exp(sQ) \exp((t-s)R)\mathbf{1}.$$

Next, let $E \subseteq E_{\boldsymbol{n}}$ be a subset of the state space, define the indicator column vector $\mathbb{1}_E$ to be 1 for the states in E and 0 for the states in E^c. Then,

$$\mathrm{P}(\boldsymbol{S}(t) \in E \text{ and } D(s) = D(t)) = \boldsymbol{\pi} \exp(sQ) \exp((t-s)R)\mathbb{1}_E,$$

and so

$$\mathrm{P}(I(t) + C(t) = k | D(s) = D(t)) = \frac{\boldsymbol{\pi} \exp(sQ) \exp((t-s)R)\mathbb{1}_{\{I+C=k\}}}{\boldsymbol{\pi} \exp(sQ) \exp((t-s)R)\mathbf{1}}$$

where $\{I+C=k\}$ represents the set of states in which the number of infectives plus carriers is equal to k.

2.3.1 Comparison of methods

The matrix exponential method is computationally much faster than the path evaluation method and works well for population sizes less than 25. However, when n is 25, the state space has 3627 elements and so the matrices $\exp(sQ)$ and $\exp((t-s)R)$ have more than 13 million entries each, which places high demands on the computer memory. Also note that since the size of the state space is proportional to n^3, the number of entries in these temporal matrices is proportional to n^6, and so this problem cannot be readily solved by simply increasing the amount of computer memory.

Although the matrix exponential method is many times faster than using the

path evaluation method described in section 2.2, the path evaluation method does have certain advantages over the matrix method. Firstly, once the coefficients C_1 and C_2 have been computed in the path evaluation method (for a given set of parameters), they provide the function $h_{\boldsymbol{n}}(\boldsymbol{x}, \boldsymbol{\theta}, t)$ for all time. This allows the function to be easily differentiated or integrated with respect to time. The matrix exponential needs to be recalculated for each time point required. Secondly, it is possible to adapt the path evaluation method to calculate other interesting functionals of the epidemic, for instance the expected severity $\mathrm{E}\left[\int_0^\infty I(t) + C(t)\,\mathrm{d}t\right]$ and the expected time to extinction $\int_0^\infty \mathrm{P}(I(t) + C(t) > 0)\,\mathrm{d}t$. Also, by evaluating the possible paths of the epidemic process, this method gives a very clear and direct understanding of the model itself, and its behaviour. However, it relies on the number of paths that the process may take being finite (and possible to compute in a reasonable amount of time) and this makes the method suitable only for epidemic models with small population sizes or small subpopulations, for instance those used in households models (see section 2.6). Next, we consider the branching process approximation to the epidemic, which is valid for both large populations and for the early stages of an epidemic in moderate populations.

2.4 Branching process approximation

As the number of susceptibles tends to infinity, the probability of a susceptible being contacted more than once in the initial phase of the epidemic becomes negligible. Therefore for moderately large n, the initial phase of the epidemic can either be modelled by a branching process, or, since the asymptomatic carriage epidemic model has the Markov property, a birth and death process with two types of individual.

It is possible to write the probability that the epidemic is over at t given no discoveries in $(s, t]$ in terms of solutions to some differential equations, which are not explicitly solvable in general. For $i, c \in \mathbb{N} \cup \{0\}$ with $i + c > 0$ and for $t \in [0, \infty)$ define

$$p_{i,c}(t) = \mathrm{P}(D(t) = D(0) | (I(0), C(0)) = (i, c))$$

and

$$r_{i,c}(t) = \mathrm{P}(D(t) = D(0) \text{ and } I(t) + C(t) = 0 | (I(0), C(0)) = (i, c)).$$

The offspring of the zeroth generation of the birth-death process can be considered as the initial ancestors of independent birth-death processes. There are no discoveries in the original process if and only if there are no discoveries in the offspring processes, and so we have that

$$\begin{aligned} p_{i,c}(t) &= p_{1,0}(t)^i p_{0,1}(t)^c, \\ r_{i,c}(t) &= r_{1,0}(t)^i r_{0,1}(t)^c. \end{aligned}$$

By conditioning on the state of the process at time Δt it is possible to derive the backward equations for these functions. For example,

$$\begin{aligned} p_{1,0}(t+\Delta t) &= \beta_{1,1}\Delta t p_{2,0}(t) + \beta_{1,2}\Delta t p_{1,1}(t) + (1-\Delta t(\beta_{1,1}+\beta_{1,2}+\gamma))p_{1,0}(t) \\ &\quad + o(\Delta t) \end{aligned}$$

which implies that

$$\begin{aligned} \frac{\mathrm{d}p_{1,0}(t)}{\mathrm{d}t} &= \beta_{1,1}p_{1,0}(t)^2 + \beta_{1,2}p_{1,0}(t)p_{0,1}(t) - (\beta_{1,1}+\beta_{1,2}+\gamma)p_{1,0}(t) \qquad (2.9) \\ \frac{\mathrm{d}p_{0,1}(t)}{\mathrm{d}t} &= \beta_{2,2}p_{0,1}(t)^2 + \beta_{2,1}p_{1,0}(t)p_{0,1}(t) - (\beta_{2,2}+\beta_{2,1}+\mu)p_{0,1}(t) + \mu \qquad (2.10) \\ \frac{\mathrm{d}r_{1,0}(t)}{\mathrm{d}t} &= \beta_{1,1}r_{1,0}(t)^2 + \beta_{1,2}r_{1,0}(t)r_{0,1}(t) - (\beta_{1,1}+\beta_{1,2}+\gamma)r_{1,0}(t) \\ \frac{\mathrm{d}r_{0,1}(t)}{\mathrm{d}t} &= \beta_{2,2}r_{0,1}(t)^2 + \beta_{2,1}r_{1,0}(t)r_{0,1}(t) - (\beta_{2,2}+\beta_{2,1}+\mu)r_{0,1}(t) + \mu \end{aligned}$$

with the boundary conditions

$$\begin{aligned} p_{1,0}(0) &= 1 \\ p_{0,1}(0) &= 1 \\ r_{1,0}(0) &= 0 \\ r_{0,1}(0) &= 0. \end{aligned}$$

Firstly notice that these equations trivially imply that $r_{1,0}(t) = 0$. This is also implied from the definition, as it is impossible for the epidemic to die out without the discovery of the initial infective. This implies that

$$\frac{\mathrm{d}r_{0,1}(t)}{\mathrm{d}t} = \beta_{2,2}r_{0,1}(t)^2 - (\beta_{2,2}+\beta_{2,1}+\mu)r_{0,1}(t) + \mu$$

which can be solved to give

$$r_{0,1}(t) = \frac{\xi_2(\xi_1 - 1) + \xi_1(1 - \xi_2)e^{-(\xi_1 - \xi_2)\beta_{2,2}t}}{\xi_1 - 1 + (1 - \xi_2)e^{-(\xi_1 - \xi_2)\beta_{2,2}t}}$$

where $\xi_1 > \xi_2$ are the two roots of the equation

$$\beta_{2,2}x^2 - (\beta_{2,2} + \beta_{2,1} + \mu)x + \mu = 0.$$

The differential equations (2.9) and (2.10) can be jointly solved numerically.

Now, by conditioning on the number of infectious individuals at time s, we can formulate the probability the epidemic is over at t given no discoveries in $(s, t]$.

$$\begin{aligned}
&\mathrm{P}(I(t) + C(t) = 0 | D(s) = D(t)) \\
&\qquad = \frac{\mathrm{P}(I(t) + C(t) = 0 \text{ and } D(s) = D(t))}{\mathrm{P}(D(s) = D(t))} \\
&\qquad = \frac{\sum_{y=0}^{\infty} r_{0,1}(t-s)^y \mathrm{P}(C(s) = y)}{\sum_{x,y=0}^{\infty} p_{1,0}(t-s)^x p_{0,1}(t-s)^y \mathrm{P}((I(s), C(s)) = (x, y))} \\
&\qquad = \frac{\Phi(0, r_{0,1}(t-s); s)}{\Phi(p_{1,0}(t-s), p_{0,1}(t-s); s)}
\end{aligned}$$

where $\Phi(u, v; t) = \mathrm{E}\left[u^{I(t)} v^{C(t)}\right]$.

The function $\Phi(u, v; t)$ satisfies the following partial differential equation,

$$\begin{aligned}
\frac{\partial \Phi(u, v; t)}{\partial t} &= \frac{\partial \Phi(u, v; t)}{\partial u}(\beta_{1,1}u^2 + \beta_{1,2}uv - (\beta_{1,1} + \beta_{1,2} + \gamma)u + \gamma) \\
&\quad + \frac{\partial \Phi(u, v; t)}{\partial v}(\beta_{2,2}v^2 + \beta_{2,1}uv - (\beta_{2,2} + \beta_{2,1} + \mu)v + \mu)
\end{aligned}$$

with the boundary conditions

$$\begin{aligned} \Phi(1,1;t) &= 1, \\ \Phi(u,v;0) &= u^i v^c. \end{aligned}$$

Unfortunately, a solution to these equations is not available in general, only for the special case considered in section 2.4.1 (see Mode, 1962). Instead, the best way to proceed is to simulate the birth-death process until time s, to estimate the joint distribution of the number of individuals alive at this time. This can then be used to approximate the generating function $\Phi(u,v;s) = \mathrm{E}\left[u^{I(s)}v^{C(s)}\right]$.

In conclusion, the probability the epidemic is over given a period without discoveries can be found by numerically solving differential equations for $p_{1,0}(t-s)$ and $p_{0,1}(t-s)$ and then simulating the birth-death process up to time s to obtain an estimate for $\Phi(u,v;s)$. However, in a special case, there is an entirely analytic solution to the problem.

2.4.1 A special case

The following argument is due to Frank Ball.

Consider the special case of the model in which infectives and carriers have the same removal rates, and the type of a new infectious individual is independent of the type of individual which created them. In this special case, both types of infectious individual behave in the same way until they are removed, at which point a proportion of them become discovered, and the rest escape detection. Although the preceeding results can still be applied, it is now possible to obtain

an entirely analytic solution to the problem. Let π denote the proportion of infectious individuals to be discovered, and $X(t)$ denote the number of infectious individuals at time t.

Grimmett and Stirzaker (2001) give the generating function of $X(t)$ to be

$$\begin{aligned}\Phi(u;t) &= \mathrm{E}\left[u^{X(t)}\right] \\ &= \begin{cases} \left(\frac{\beta t(1-u)+u}{\beta t(1-u)+1}\right)^{X(0)} & \gamma = \beta, \\ \left(\frac{\gamma(1-u)-(\gamma-\beta u)e^{-t(\beta-\gamma)}}{\beta(1-u)-(\gamma-\beta u)e^{-t(\beta-\gamma)}}\right)^{X(0)} & \gamma \neq \beta, \end{cases}\end{aligned}$$

where infectious individuals are created with rate β and removed with rate γ. By deriving and solving the backward equations, we find that

$$\begin{aligned} p(t) &= \mathrm{P}(D(t) = D(0) | X(0) = 1) \\ &= \frac{\zeta_2(\zeta_1 - 1) + \zeta_1(1-\zeta_2)e^{-(\zeta_1-\zeta_2)\beta t}}{\zeta_1 - 1 + (1-\zeta_2)e^{-(\zeta_1-\zeta_2)\beta t}} \\ r(t) &= \mathrm{P}(D(t) = D(0) \text{ and } X(t) = 0 | X(0) = 1) \\ &= \frac{\zeta_1\zeta_2(1 - e^{-(\zeta_1-\zeta_2)\beta t})}{\zeta_1 - \zeta_2 e^{-(\zeta_1-\zeta_2)\beta t}} \end{aligned}$$

where $\zeta_1 > 1 > \zeta_2 > 0$ are the roots of the equation

$$\beta z^2 - (\beta + \gamma)z + \gamma\pi = 0.$$

Finally,

$$\mathrm{P}(X(t) = 0 | D(s) = D(t)) = \frac{\Phi(r(t-s); s)}{\Phi(p(t-s); s)}.$$

2.5 Effects of parameter changes

This section numerically explores the effect of the parameters on the probability the epidemic is over given a period without discoveries for both the epidemic model and the branching process approximation.

The parameters used in this section have been chosen to cover as broad a range of cases as possible. However, since it is impossible to cover the whole parameter space, this section focuses on changing s, t, R_* and n. Unless otherwise stated it is assumed that infectives are twice as infectious as carriers, as this is thought to be the case for influenza-like illnesses for example avian influenza (Ferguson *et al.*, 2005). This is because symptoms like coughing and sneezing clearly increase the transmissibility of airborne infections. Where possible it is assumed that symptomatic individuals are removed at twice the rate of carriers. This assumption does not indicate a difference in the duration of infection within the two types of individual, but instead represents a difference in the *effective* infectious period, as symptomatic individuals are likely to withdraw to the home and stop mixing. Also, infectives are observed upon removal and so this is equivalent to assuming that once they are discovered to have the infection, they are prevented from making any further infectious contacts, either through treatment or isolation. It is always assumed that infectives have infectious periods with mean length one, so the units of time can be interpreted as multiples of this period, and therefore have some interpretation in the context of the epidemic.

Figure 2.1 shows the effect of increasing the length of the period of no discoveries on the probability the epidemic is over given $D(1/2) = D(t)$ for several values of

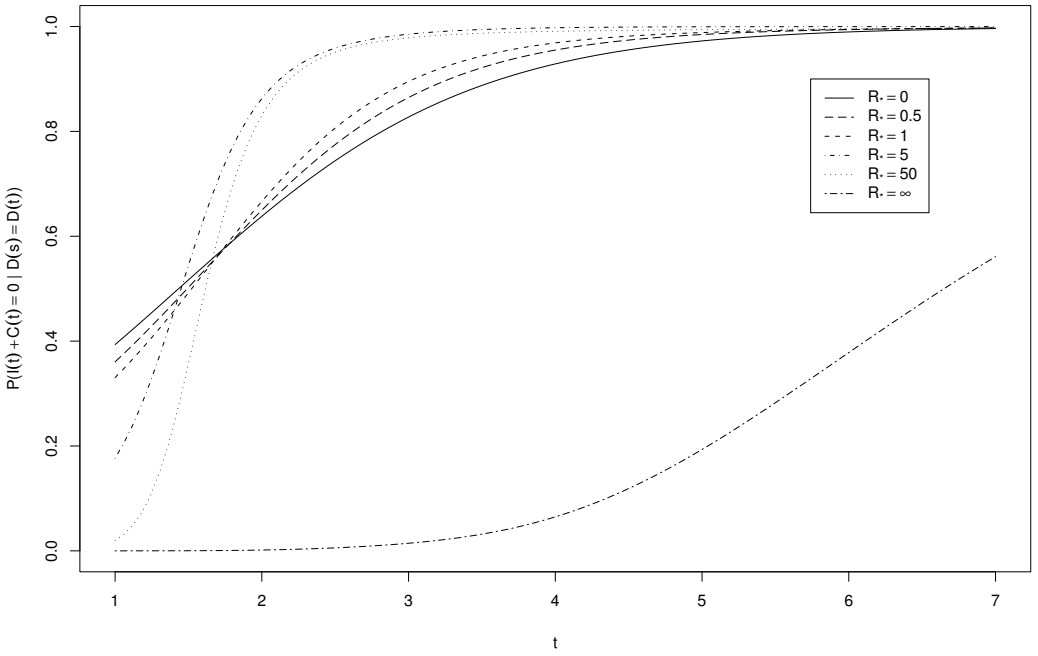

Figure 2.1: $\mathrm{P}(I(t) + C(t) = 0 | D(s) = D(t))$ against t for $s = 1/2$, $(n, i, c) = (20, 1, 0)$, $(\beta_{1,1}, \beta_{1,2}, \beta_{2,1}, \beta_{2,2}) = \frac{\lambda}{n}(0.6, 0.4, 0.2, 0.3)$, $\gamma = 1$ and $\mu = 1/2$.

R_*. The value of R_* is changed by altering the parameter λ, which determines the infectious contact rates as $(\beta_{1,1}, \beta_{1,2}, \beta_{2,1}, \beta_{2,2}) = \frac{\lambda}{n}(0.6, 0.4, 0.2, 0.3)$. The curve for $R_* = \infty$ is calculated by setting λ to be very large.

When the period of no discoveries is small this gives very little information about the state of the model, and so epidemics with smaller values of R_* are more likely to be extinct than ones with larger values of R_*. However, as the length of the period of no discoveries increases, more information is gained for models with moderately large values of R_*. These models have the most uncertainty in their behaviour, as they can either die out rapidly or persist with a major outbreak, and therefore a longer period without discoveries suggests that the former of these has occurred. When R_* becomes very large, a period

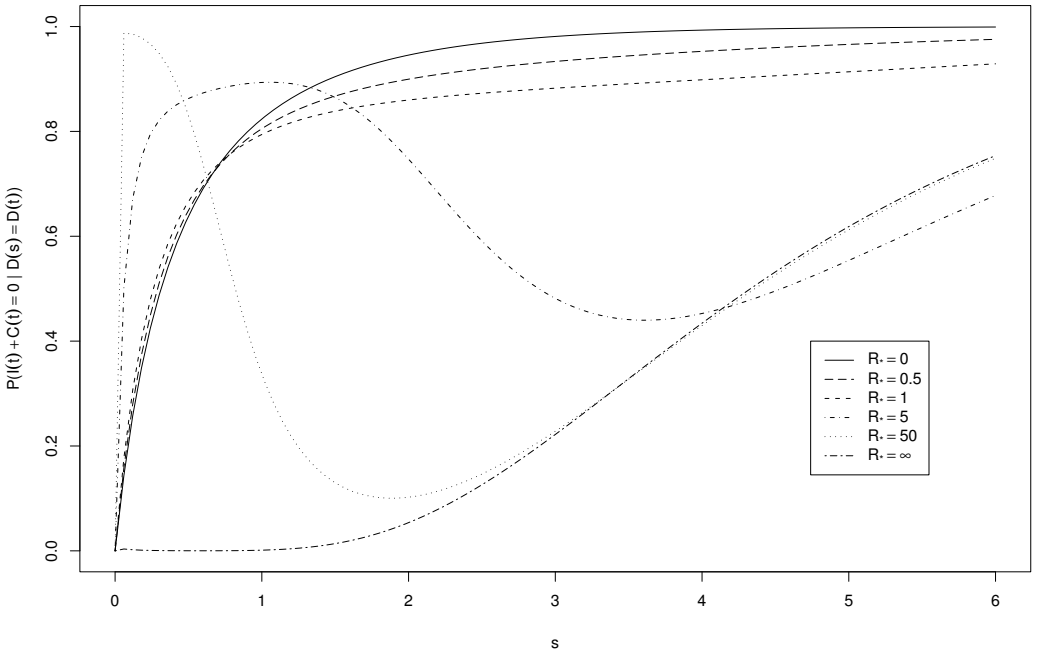

Figure 2.2: $\mathrm{P}(I(t) + C(t) = 0 | D(s) = D(t))$ against s for $t = s + 1$, $(n, i, c) = (20, 1, 0)$, $(\beta_{1,1}, \beta_{1,2}, \beta_{2,1}, \beta_{2,2}) = \frac{\lambda}{n}(0.6, 0.4, 0.2, 0.3)$, $\gamma = 1$ and $\mu = 1/2$.

containing no discoveries gives much less information about the model because the probability of extinction is so small. Instead it suggests that the infection is still present in carriers.

Figure 2.2 demonstrates the effect of altering the start time of a fixed length period of no discoveries on the probability the epidemic is over given $D(s) = D(s + 1)$. Since the initial infective must be discovered before the epidemic can cease, all of the curves begin at zero. In the first stage of the graph, the epidemics most likely to be over are the ones with moderately large values of R_*, as for these epidemics the period of no discoveries is most informative. However, as s increases a period without discoveries becomes less informative, as carriers have longer infectious periods and are more likely to persist. As R_*

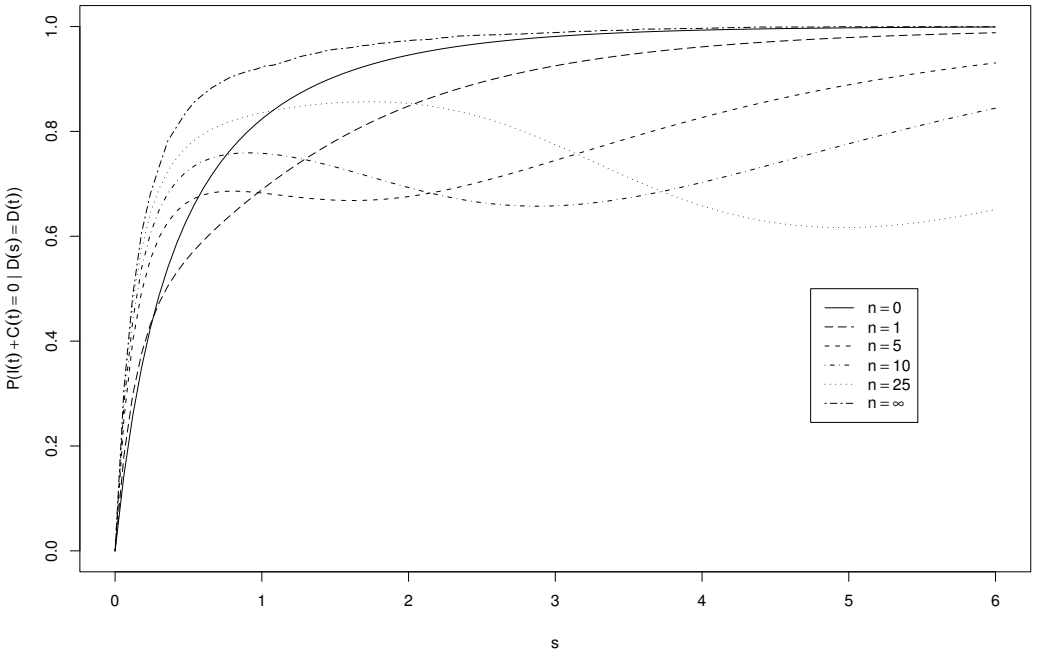

Figure 2.3: $\mathrm{P}(I(t) + C(t) = 0 | D(s) = D(t))$ against s for $t = s + 1$, $R_* = 3$, $(i, c) = (1, 0)$, $(\beta_{1,1}, \beta_{1,2}, \beta_{2,1}, \beta_{2,2}) = \frac{\lambda}{n}(0.6, 0.4, 0.2, 0.3)$, $\gamma = 1$ and $\mu = 1/2$.

becomes very large the behaviour is very different. Despite the period of no discoveries, the epidemic is extremely unlikely to be over in the early stages. However when s increases, the probability the epidemic is over rapidly approaches one, as all of the population is infected right at the beginning of the epidemic.

Figure 2.3 shows the effect of increasing the population size on the probability the epidemic is over given a period without discoveries. For $n = \infty$, 10,000 simulations of the branching process up to time s were used to calculate the joint distribution of the number of infectives and carriers, and the probability of no discoveries in $(0, t - s]$ was found by numerically solving the differential equations (2.9) and (2.10).

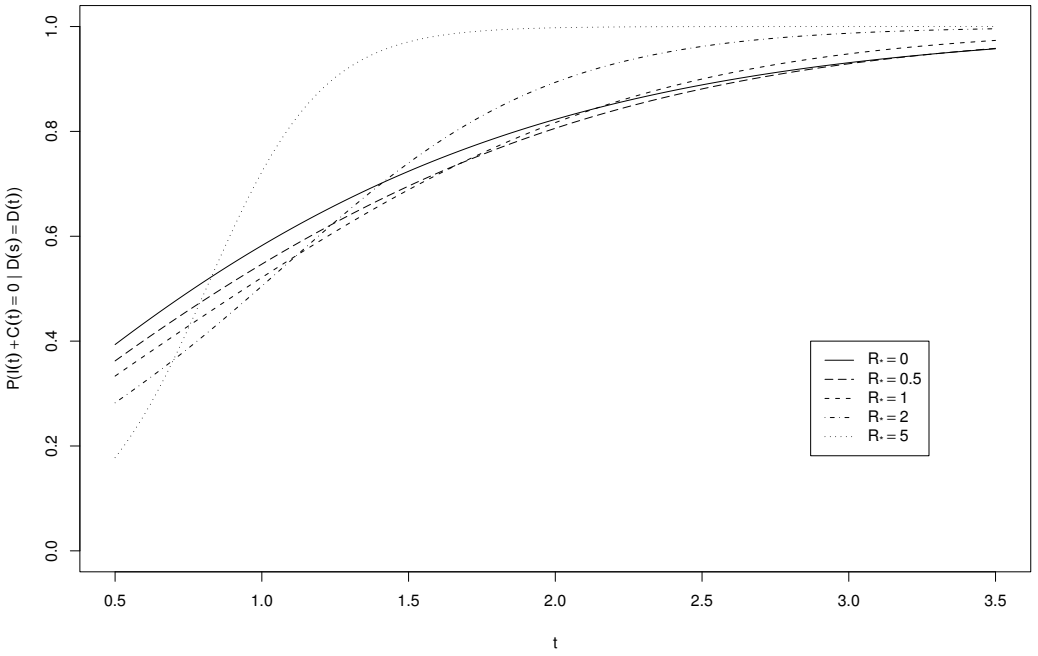

Figure 2.4: $\mathrm{P}(I(t) + C(t) = 0 | D(s) = D(t))$ against t for $s = 1/2$, $i = 1$, $\pi = 1/2$ and $\gamma = \mu = 1$.

As in figure 2.2, the period of no discoveries gives most information at the beginning of the epidemic. As n increases, the potential for more infections increases and so a period without discoveries makes the epidemic even more likely to be over. However, as s increases, the effect of the period of no discoveries begins to diminish for all of the models with finite n because the supply of susceptibles runs out. Those with smallest n are most affected as these models are unable to sustain a long epidemic. When n is infinite however, the information given by the period of no discoveries only increases the likelihood that the epidemic is over, until it approaches one. Without the period of no discoveries, this curve would tend to the probability of extinction for the branching process, which is $1/3$. It is important to notice that the curve for $n = \infty$ is an upper bound for the finite n cases, and that it is often very close to the curves for finite n. The

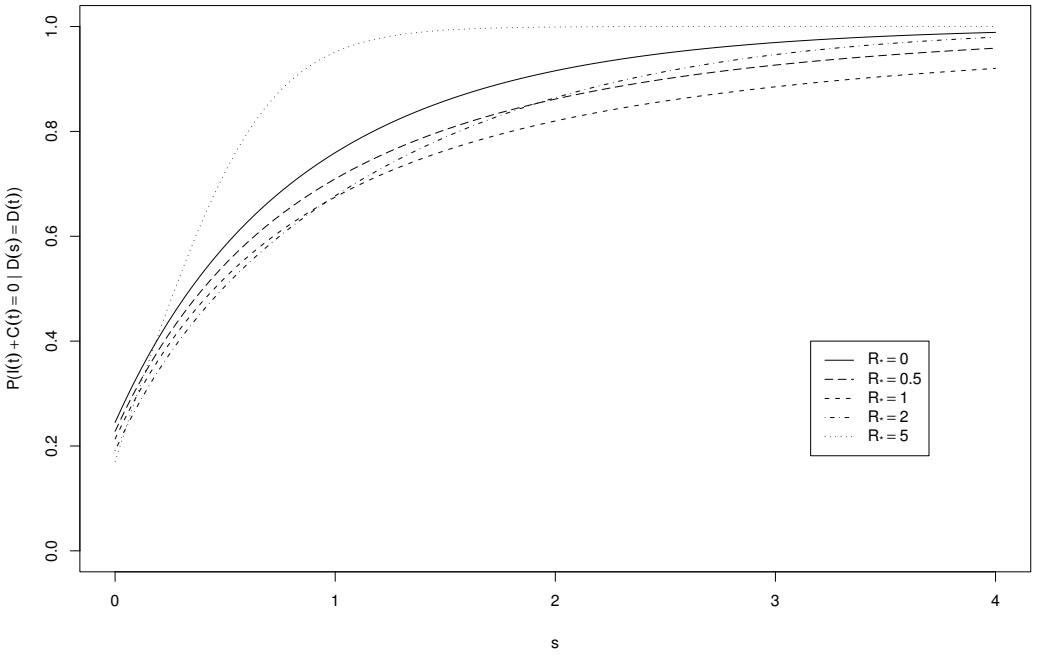

Figure 2.5: $\mathrm{P}(I(t) + C(t) = 0 | D(s) = D(t))$ against s for $t = s + 1/2$, $i = 1$, $\pi = 1/2$ and $\gamma = \mu = 1$.

branching process can therefore be used as a reasonable approximation to the epidemic process, particularly in the early stages of the epidemic.

Figures 2.4 and 2.5 are the analogues of figures 2.1 and 2.2 for the special case of the branching process model discussed in section 2.4.1. Here the parameter π represents the probability that a newly infected individual becomes an infective.

The trends visible in figure 2.4 agree with those in figure 2.1 with one exception. For the branching process, the probability the epidemic is over given a period of no discoveries continues to increase as R_* is increased. This is because there is no limit on the number of infectives in the branching process, so as R_* increases, a period without discoveries suggests that the epidemic is over more and more strongly.

In figure 2.5, the probability the epidemic is over given a period of no discoveries is increasing in s. This strongly contrasts with figure 2.2, in which the information $\{D(s) = D(s + 1/2)\}$ affected the probability the epidemic is over less as s was increased. This is because in the branching process model the number of susceptibles is not limited, and so it is possible for the epidemic to be sustained for all time. Interestingly, the probability the epidemic is over given no discoveries tends to one the slowest when $R_* = 1$. This is likely to be because the expected number of infectives remains constant when $R_* = 1$. When s is large, subcritical branching processes are likely to be extinct and supercritical process will either be extinct or contain a large number of infectives. This means that the event $\{D(s) = D(s + 1/2)\}$ is very informative for supercritical processes, and suggests extinction.

2.6 Structured populations

The asymptomatic carriage epidemic model assumes that the population is homogeneously mixing, which is not particularly realistic. An easy way to remove this assumption is to divide the population into households and introduce two levels of mixing into the model. Unfortunately, this increases the size of the state space for a given population size, and reduces still further the population sizes for which it is feasible to perform calculations. Instead it will be assumed that a population divided into households experiences some approximately constant source of infection from elsewhere for some fixed time, which can be thought, approximately, as the duration of the epidemic season. After the external source of infection is withdrawn the epidemic proceeds within the households. It is assumed throughout that the number of between household contacts is small enough to be ignored compared with the household contacts and external infections, and therefore the households behave independently. Other papers to consider this kind of independent households model include Addy *et al.* (1991) and Demiris and O'Neill (2005).

Let m be the number of households. If the are no discoveries in the whole population, then there are no discoveries in any one household, and since the households behave independently we have that

$$\begin{aligned} &\mathrm{P}\left(\sum_{j=1}^{m} I_j(t) + C_j(t) = 0 \middle| D_j(s) = D_j(t)\ \forall j\right) \\ &\qquad = \prod_{j=1}^{m} \mathrm{P}(I_j(t) + C_j(t) = 0 | D_j(s) = D_j(t)) \end{aligned}$$

where the subscript j denotes the household with index j. Thus, we need

consider only a single household.

Consider a household of size n, and assume that initially there are no infectious individuals. In the time interval $(0, w]$ each member of the household is contacted from outside the household at the points of a Poisson process with rate $\alpha_1 + \alpha_2$ and once contacted become an infective with probability $\alpha_1/(\alpha_1 + \alpha_2)$. The within household contact rates are given by B as before. Thus, infectives are created at a rate $(\alpha_1 + \beta_{1,1}I(t) + \beta_{2,1}C(t))S(t)$ and carriers are created at a rate $(\alpha_2 + \beta_{1,2}I(t) + \beta_{2,2}C(t))S(t)$. As before infectives and carriers are removed at rate γ and μ respectively. After time w, the source of external infection is withdrawn and the vector $\boldsymbol{\alpha} = (\alpha_1, \alpha_2)$ is set to zero.

Let $Q_{\boldsymbol{\alpha}}$ denote the generator matrix of the process before time w, and let Q denote it after time w, when $\boldsymbol{\alpha}$ is set to zero. Similarly to section 2.3, define $R_{\boldsymbol{\alpha}}$ and R to be the restricted generator matrices before and after w; where for $u \neq v$, $r_{u,v}$ represents the rate at which the process goes from state u to state v with no discoveries, and $r_{u,u} = q_{u,u}$. By conditioning on the state of the process at times w and s it is easy to show that

$$
\begin{aligned}
&\mathrm{P}(I(t) + C(t) = k | D(s) = D(t)) \\
&= \frac{\mathrm{P}(I(t) + C(t) = k \text{ and } D(s) = D(t))}{\mathrm{P}(D(s) = D(t))} \\
&= \begin{cases}
\dfrac{\boldsymbol{\pi} \exp(sQ_{\boldsymbol{\alpha}}) \exp((t-s)R_{\boldsymbol{\alpha}}) \mathbb{1}_{\{I+C=k\}}}{\boldsymbol{\pi} \exp(sQ_{\boldsymbol{\alpha}}) \exp((t-s)R_{\boldsymbol{\alpha}}) \mathbf{1}} & s < t < w \\
\dfrac{\boldsymbol{\pi} \exp(sQ_{\boldsymbol{\alpha}}) \exp(w-s)R_{\boldsymbol{\alpha}}) \exp((t-w)R) \mathbb{1}_{\{I+C=k\}}}{\boldsymbol{\pi} \exp(sQ_{\boldsymbol{\alpha}}) \exp(w-s)R_{\boldsymbol{\alpha}}) \exp((t-w)R) \mathbf{1}} & s < w < t \\
\dfrac{\boldsymbol{\pi} \exp(wQ_{\boldsymbol{\alpha}}) \exp(s-w)Q) \exp((t-w)R) \mathbb{1}_{\{I+C=k\}}}{\boldsymbol{\pi} \exp(wQ_{\boldsymbol{\alpha}}) \exp(s-w)Q) \exp((t-w)R) \mathbf{1}} & w < s < t
\end{cases}
\end{aligned}
$$

where $\boldsymbol{\pi}$ is a row vector representing the initial distribution of the household, $\mathbf{1}$ is a column vector of ones, $\mathbb{1}_E$ is a column vector with $\mathbb{1}_E(u) = 1$ if $u \in E$ and

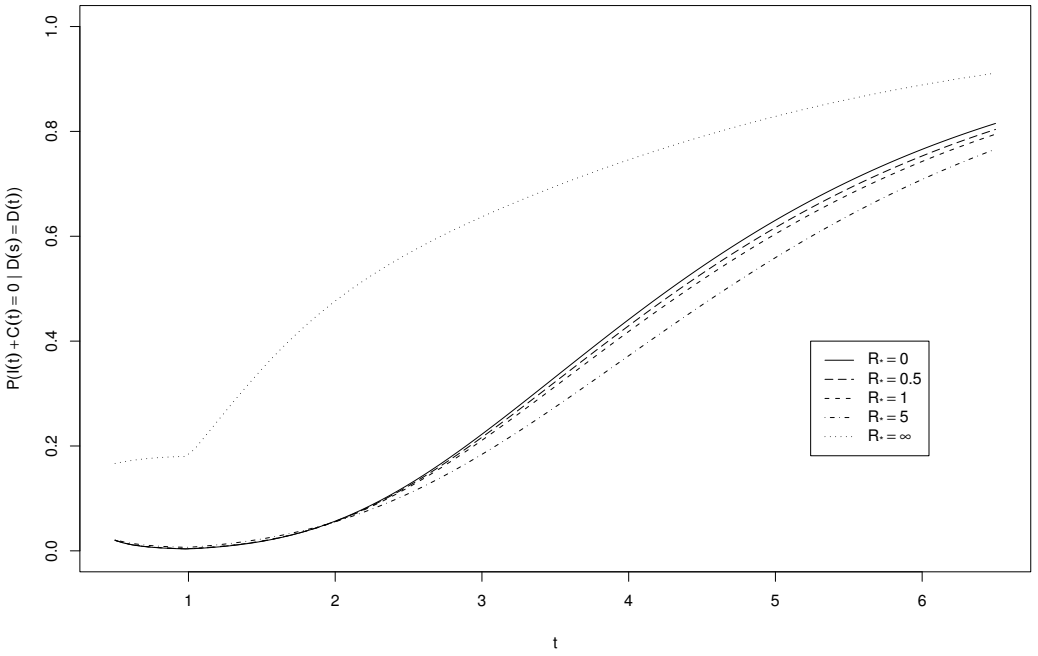

Figure 2.6: $\mathrm{P}(I(t) + C(t) = 0 | D(s) = D(t))$ against t for $w = 1$, $s = 1/2$, $(n, i, c) = (6, 0, 0)$, $\boldsymbol{\alpha} = (5, 5)$, $(\beta_{1,1}, \beta_{1,2}, \beta_{2,1}, \beta_{2,2}) = \frac{\lambda}{n}(0.6, 0.4, 0.2, 0.3)$, $\gamma = 1$ and $\mu = 1/2$.

zero otherwise and $\{I + C = k\}$ is the set of states with k infectious individuals.

2.6.1 Effects of parameter changes

Figure 2.6 shows the effect of increasing the length of the period of no discoveries on the probability the epidemic is over given $D(1/2) = D(t)$. When t is less than w the probability the epidemic is over is kept low by the possibility of new infections from outside occurring shortly before t. Once t is increased above w, extinction becomes more likely. The graphs do not approach one very quickly because there is quite a high probability that an infective is active at time s or created in $(s, w]$, and if there are no discoveries in $(s, t]$ this infective must still

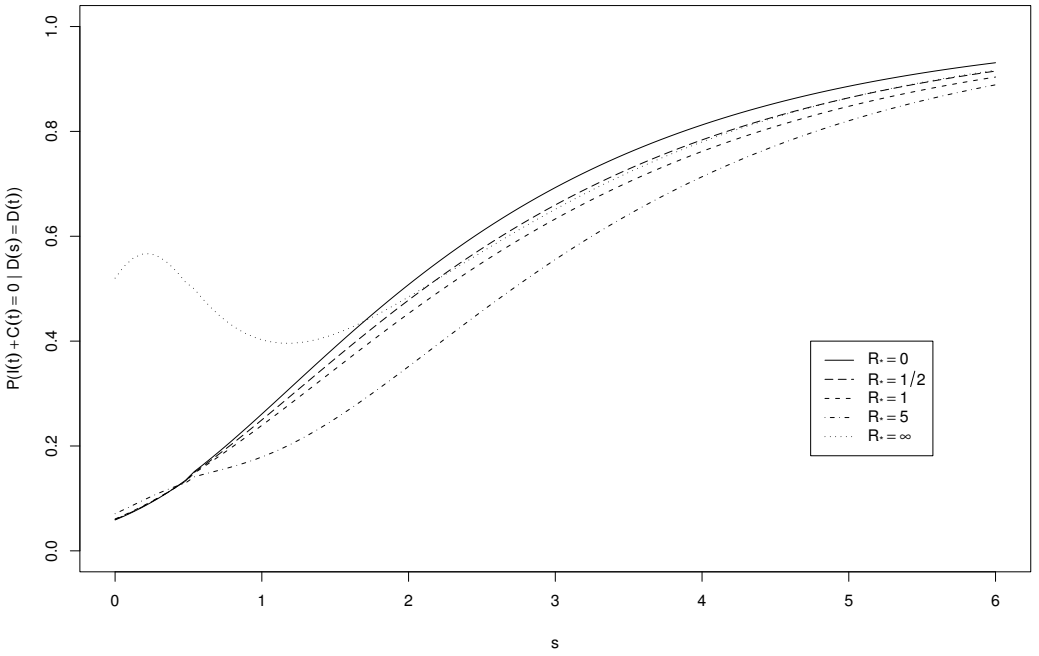

Figure 2.7: $\mathrm{P}(I(t) + C(t) = 0 | D(s) = D(t))$ against s for $w = 1/2$, $t = s + 1$, $(n, i, c) = (6, 0, 0)$, $\boldsymbol{\alpha} = (5, 5)$, $(\beta_{1,1}, \beta_{1,2}, \beta_{2,1}, \beta_{2,2}) = \frac{\lambda}{n}(0.6, 0.4, 0.2, 0.3)$, $\gamma = 1$ and $\mu = 1/2$.

exist at t.

The probability the epidemic is over at $s + 1$ given no discoveries in $(s, s + 1]$ is plotted against s in figure 2.7. Like figure 2.2, when s is small the epidemics with the largest values of R_* are most likely to be extinct because no discoveries are observed in the early stages. As s increases the effect of this period without discoveries begins to diminish and the probabilities re-order themselves so that the values of R_* that are likely to cause epidemics with long duration are least likely to be extinct. Unlike figure 2.2 the graphs do not begin at zero as there is no longer definitely an initial infective that must be discovered before the epidemic dies out.

2.7 Stopping time problem

This section considers a variation on the original problem, in which the epidemic process is stopped at the first time at which no discoveries have been made in the last t time units. Defining

$$T_t = \inf\{u \geq t : D(u) = D(u-t)\},$$

we will seek to evaluate

$$\mathrm{P}(I(T_t) + C(T_t) = 0) \;=\; \sum_{d \in D} \mathrm{P}(I(T_t) + C(T_t) = 0|d)\mathrm{P}(d)$$

where d is the path that the process takes through the state space and D is the set of all possible paths through the state space. Each of these paths is of finite length and ends at an absorbing state of the form $(x, 0, 0)$ for $x \in \{0, \ldots, n\}$. Thus, $\mathrm{P}(I(T_t) + C(T_t) = 0|d)$ is the probability that the waiting times between discovery events in the path are all less than t. The probability the process takes path d is given by $\mathrm{P}(d) = \prod_{j=0}^{L-1} a_j/b_j$ where a_j and b_j are defined in equations (2.1) and (2.2) respectively, and L is the length of path d.

Recall that a path d of length L consists of a sequence of states $\{\boldsymbol{s}_0, \ldots, \boldsymbol{s}_L\}$. If there are K discovery events in the path, then d can be broken down into $K+1$ subpaths $d_0, \ldots, d_K$ separated by discovery events. Thus, $d = \{d_0, \ldots, d_K\}$. For example the path

$$d \;=\; \{(3,2,0),(3,1,0),(2,2,0),(2,1,0),(2,0,0)\}$$

with $L = 4$ contains $K = 3$ discoveries and so

$$\begin{aligned} d_0 &= \{(3,2,0)\} \\ d_1 &= \{(3,1,0),(2,2,0)\} \\ d_2 &= \{(2,1,0)\} \\ d_3 &= \{(2,0,0)\} \end{aligned}$$

with lengths $L_0 = 0$, $L_1 = 1$, $L_2 = 0$, $L_3 = 0$ and we see that $L = K + \sum_{k=0}^{K} L_k$. For $k = 0, \ldots, K$ and $j = 0, \ldots, L_k$ let $\boldsymbol{s}_{k,j}$ denote the jth state visited in the path d_k. Let $q(\boldsymbol{x})$ denote the rate at which the process leaves state $\boldsymbol{x}$ so that

$$q(\boldsymbol{x}) = ((\beta_{1,1} + \beta_{1,2})x_2 + (\beta_{2,1} + \beta_{2,2})x_3)x_1/n + \gamma x_2 + \mu x_3.$$

Since the waiting time in state $\boldsymbol{x}$ is distributed $\text{Exp}(q(\boldsymbol{x}))$, we have

$$\begin{aligned} \text{P}(I(T_t) + C(T_t) = 0|d) &= \left(\prod_{k=0}^{K-1} \text{P}(\text{path } d_k \text{ lasts less than } t)\right) \\ &\quad \times \text{P}(\text{first } L_K - 1 \text{ steps of path } d_K \text{ last less than } t) \\ &= \left(\prod_{k=0}^{K-1} \text{P}\left(\sum_{j=0}^{L_k} W_{k,j} < t\right)\right) \text{P}\left(\sum_{j=0}^{L_K - 1} W_{K,j} < t\right), \end{aligned}$$

where for $k = 0, \ldots, K$ and $j = 0, \ldots, L_K$, $W_{k,j} \sim \text{Exp}(q(\boldsymbol{s}_{k,j}))$ and the $W_{k,j}$ are independent.

P203 of Rényi (1970) states that if X_j $(j = 1, \ldots, n)$ are independent exponential distributions with distinct intensities λ_j then $Y = \sum_{j=1}^{n} X_j$ has probability

density function

$$f_Y(y) = (-1)^{n-1}\lambda_1 \dots \lambda_n \sum_{j=1}^{n} \frac{\exp(-\lambda_j y)}{\prod_{k \neq j} \lambda_j - \lambda_k}$$

for $y > 0$ and therefore

$$\mathrm{P}(Y < y) = (-1)^{n-1} \sum_{j=1}^{n} (1 - \exp(-\lambda_j y)) \prod_{k \neq j} \frac{\lambda_k}{\lambda_j - \lambda_k} \tag{2.11}$$

which can be used to calculate $\mathrm{P}(I(T_t) + C(T_t) = 0)$ if $q(\boldsymbol{x}) \neq q(\boldsymbol{y})$ for every pair of states $\boldsymbol{x} \neq \boldsymbol{y}$ in every possible path between discoveries. If this is not the case, the result can still be found by separating any equal rates by a factor $\epsilon > 0$ and then taking the limit $\epsilon \to 0$.

2.7.1 Effects of parameter changes

The probability that the epidemic is over at time T_t against t is given in figure 2.8. Interestingly there is very little variability for different values of R_*, which is probably due to the small population size. As with the other path evaluation methods, calculating this figure was computationally very time consuming - taking over four hours for a population of size seven. Also, due to the massive increase in the number of paths, when n is increased by one the computation time increases by about a factor of ten. This leads us to look for an analogous result for the branching process approximation to this epidemic model.

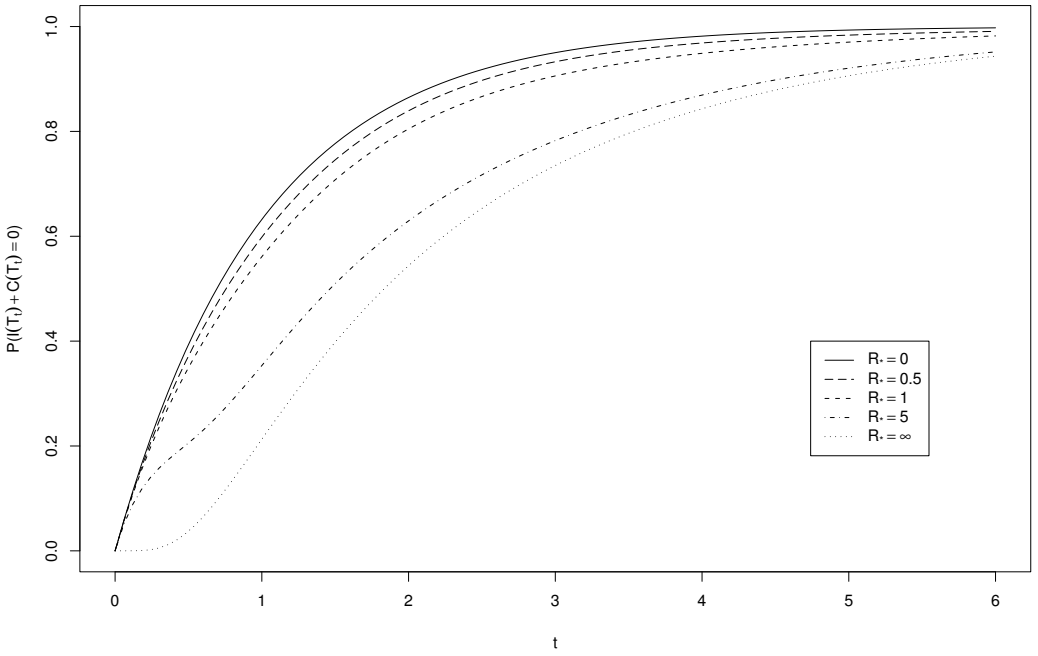

Figure 2.8: $\mathrm{P}(I(T_t)+C(T_t)=0)$ against t for $(n,i,c)=(6,1,0)$, $\gamma=1$, $\mu=1/2$ and $(\beta_{1,1},\beta_{1,2},\beta_{2,1},\beta_{2,2})=\frac{\lambda}{n}(0.6,0.4,0.2,0.3)$.

2.7.2 Branching process approximation

For the epidemic model, the method used to find $\mathrm{P}(I(T_t)+C(T_t)=0)$ cannot be extended in full generality to the branching process approximation. It relies on finding every possible path the process can take between two discovery events, and there are infinitely many such paths for a branching process. Progress is possible for the special case of the branching process model in which there is a single type of infective that is observed upon removal with probability one.

Since the infectious periods have an exponential distribution, the branching process approximation to the epidemic model is a linear birth-death process. Let $I(t)$ represent the number of individuals in the process so that births occur at a rate $\beta I(t)$ and deaths occur at a rate $\gamma I(t)$. After their 'death' individuals

enter a removed category called the discovered category, represented by the process $\{D(t) : t \geq 0\}$. As before define

$$T_t = \inf\{u \geq t : D(u) = D(u-t)\}$$

and we seek the probability that the process is extinct at this stopping time, $\mathrm{P}(I(T_t) = 0)$. Embedded within this continuous time birth-death process is a discrete time Markov chain. Let $X_0 = I(0)$ and for $n \in \mathbb{N}$ define X_n to be the number of infectives just after the nth discovery event. This embedded process satisfies the relation

$$X_{n+1} \sim \begin{cases} X_n - 1 + Y & X_n > 0, \\ 0 & X_n = 0, \end{cases} \tag{2.12}$$

where $\mathrm{P}(Y = k) = \frac{\beta\gamma^k}{(\beta+\gamma)^{k+1}}$ for $k = 0, 1, \ldots$.

This follows from the fact that the probability of having a birth before a death is equal to

$$\frac{\beta I(t)}{\beta I(t) + \gamma I(t)} = \frac{\beta}{\beta + \gamma}$$

which is independent of $I(t)$, and therefore the number of births before a death (assuming $X_n > 0$) has the geometric distribution given by Y.

First, we use the embedded process X_n to show that $\mathrm{P}(T_t < \infty) = 1$.

$$\begin{aligned} \mathrm{P}(T_t = \infty) &= \mathrm{P}(\text{the time between every discovery is less than } t) \\ &\leq \mathrm{P}(\text{the time until the first event after a discovery is less than } t) \\ &= \mathrm{E}\left[\prod_{n=0}^{\infty}(1 - \exp\{-X_n(\beta+\gamma)t\})\right] \\ &= 0 \end{aligned}$$

since the product is zero if for some n, $X_n = 0$; and zero if $X_n > 0$ for all n, as these are complimentary events.

Therefore, $\mathrm{P}(T_t < \infty) = 1$. It is now clear what we mean by $\mathrm{P}(I(T_t) = 0)$, since the stopping time T_t is almost surely finite.

Let $x_u = \mathrm{P}(I(T_t) = 0 | X_0 = u)$ and $y_{u,v} = \mathrm{P}(Y_{u,v} < t, X_1 = v | X_0 = u)$, where $Y_{u,v}$ is the time taken for $X_0 = u$ to become $X_1 = v$. Since the only path from u to v ending in the first discovery is

$$\{u, u+1, \ldots, v, v+1, v\},$$

then

$$Y_{u,v} = \sum_{k=u}^{v} W_k,$$

where $W_k \sim \mathrm{Exp}(k(\beta+\gamma))$ and the W_k are independent.

From equation (2.12) we see that

$$y_{u,v} = \left(\frac{\beta}{\beta+\gamma}\right)^{v-u+1} \left(\frac{\gamma}{\beta+\gamma}\right) \mathrm{P}(Y_{u,v} < t)$$

and $\mathrm{P}(Y_{u,v} < t)$ is given by equation (2.11).

By analysing the first jump of the process X_n and by invoking the Markov property we see that

$$x_u = \sum_{v=u-1}^{\infty} y_{u,v} x_v. \tag{2.13}$$

In order to solve this equation we truncate the infinite state space to $\{0, 1, \ldots, N\}$, where state N is an absorbing state considered to be the birth-death process tending to infinity. Clearly $x_0 = \mathrm{P}(I(T_t) = 0 | I(0) = 0) = 1$, but

since we have also shown that $\mathrm{P}(T_t < \infty) = 1$ it makes sense to assume that $x_N = 0$. Thus, equation (2.13) becomes

$$x_u = \sum_{v=u-1}^{N} y_{u,v} x_v$$

for $u = 1, \ldots, N-1$. In order to satisfy the law of total probability, $y_{u,v}$ must be modified so that

$$y_{u,N} = \left(\frac{\beta}{\beta+\gamma}\right)^{N-u+1} \mathrm{P}(Y_{u,N} < t).$$

Thus, we have $N+1$ linear equations in the $N+1$ unknowns $x_0, \ldots, x_N$ which can be easily solved to give

$$\boldsymbol{x} = (I_{N+1} - Y)^{-1}\boldsymbol{w}$$

where $\boldsymbol{x}$ and $\boldsymbol{w}$ are column vectors; $y_{0,v} = y_{N,v} = 0$ for $v = 0, \ldots, N$; I_{N+1} is the $(N+1) \times (N+1)$ identity matrix and

$$w_u = \begin{cases} 1 & u = 0, \\ 0 & u > 0. \end{cases}$$

2.7.3 Effects of parameter changes

Figure 2.9 shows the probability that the birth-death process is extinct at the stopping time T_t against t. Notice that as t is increased, the curves rapidly tend to the extinction probability for the birth-death process. When t is small, the process with $R_* = 0$ is the most likely to be extinct at T_t as there can be no new individuals. However, as t is increased above the expected infectious

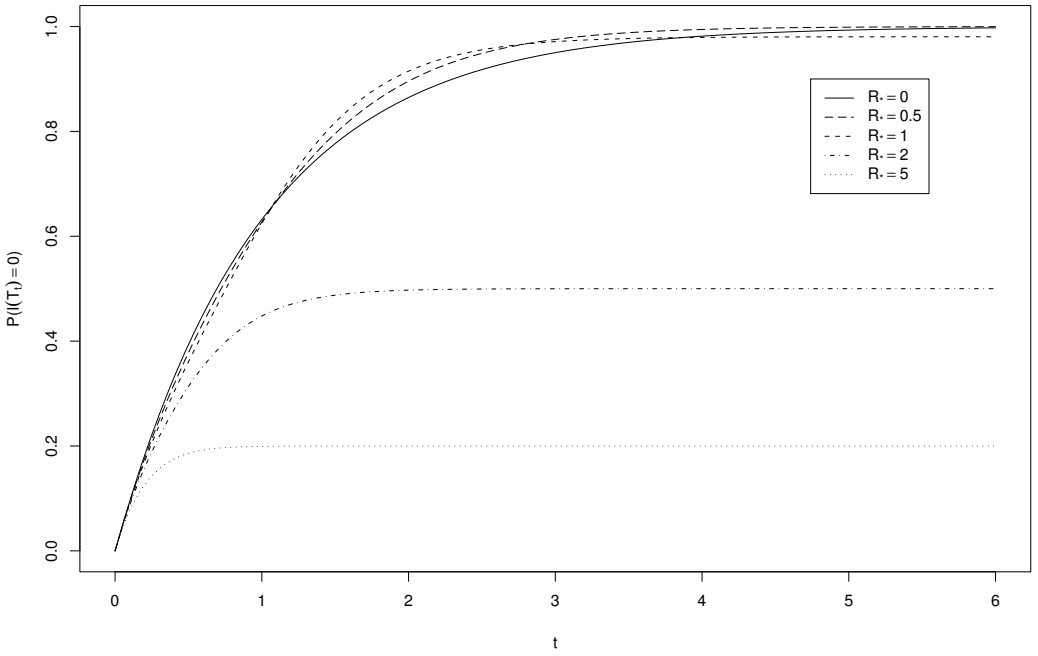

Figure 2.9: $\mathrm{P}(I(T_t) = 0)$ against t for $I(0) = 1$, $\gamma = 1$ and $N = 50$.

period length one, the information given by observing no discoveries for a period t makes extinction more likely when $0 < R_* \leq 1$, where there can be some further infections. This appears to contrast with the epidemic version (figure 2.8), in which the probability the epidemic is over at T_t is decreasing in R_*, however, when all of the discoveries are observed figure 2.8 also has the property that increased potential for infections makes extinction more likely at T_t.

Finally notice that the curve for $R_* = 1$ does not quite approach its extinction probability of one. This curve is affected by the truncation of the state space more than any of the others as it is the most likely to reach state N and yet still become extinct. Thus, its asymptote gives an indication of how good the approximation is.

2.8 Conclusion and extensions

This chapter considers an epidemic model that has two types of infectious individual: symptomatic infectives that are observed (discovered) upon removal, and asymptomatic carriers that are never observable. The aim is to find the probability the epidemic has died out if no discoveries have been observed for a certain period of time.

Two methods of finding this probability are considered: the path evaluation method and the matrix exponential method. The path evaluation method is very flexible and develops an understanding of the model, however it assumes that the eigenvalues of the model are distinct and is computationally very difficult for populations larger than 12. The matrix exponential method is faster, but still computationally difficult for populations larger than 25. These methods are therefore useful for small population epidemics, and subepidemics within a larger model for instance the independent households model considered in section 2.6.

This leads us to study the branching process approximation to the epidemic model, valid for large population sizes. Here the probability the epidemic is over given a period without discoveries can be found by simulating the branching process, and numerically solving a pair of differential equations. For the special case of the branching process model in which infectives and carriers have the same infectious period distribution and an infectious individual's type is independent of the type that infected them, an explicit solution exists.

Finally, a stopping time version of the problem was proposed, in which the epidemic was stopped at the first time at which no discoveries have been observed

for t time units. The probability that the epidemic is over at this stopping time was found by evaluating all possible paths, and this was computationally feasible for populations of size 7 and smaller. For the branching process approximation to this model the number of possible paths is infinite, and so no progress was made in general. However, for the special case in which there is a single type of infective which is observed on removal, the probability the epidemic is over at the stopping time can be found once the state space is truncated.

Throughout this chapter it is assumed that the infectious period distributions are exponential. This is usually unrealistic for human diseases, although relaxing this assumption makes analysis of the model more difficult. Some progress may be possible if the infectious periods have a fixed length, particularly for very small populations. It may also be possible to make progress after relaxing the assumption that symptomatic individuals are observed at the instant of removal. Adding exponentially distributed latent periods increases the realism and the complexity of the model, and therefore reduces the population sizes for which calculations are feasible.

Chapter 3

Modelling the effects of a delay in intervention

3.1 Motivation

The two main aims of epidemic modelling are to develop an understanding of the large-scale effects caused by interactions and properties of the disease at the individual level; and to develop and assess strategies for preventing or restricting the spread of an epidemic. This chapter upholds both of these aims by studying the time delay between observing the presence of a disease and implementing measures targeted towards its containment. This delay at the local level has global ramifications when the effectiveness of the intervention is compromised, and therefore any intervention strategy seeking to reduce the potency of an epidemic must attempt to minimise the delay prior to the intervention.

There are many different kinds of intervention that can be applied to epidemics,

but they fall into three main categories. The first type of intervention aims to reduce the susceptibility of uninfected individuals, for instance vaccinating or giving pre-emptive antiviral prophylaxis to individuals at risk of infection. The second type seeks to reduce the infectiousness of individuals who have already contracted the disease, for example antibiotic or antiviral treatments. The third type of intervention attempts to minimise the contact between infectious and susceptible individuals, for instance by isolating infectious individuals at home or in hospitals, or by more drastic measures including closing schools or cancelling public gatherings like football matches.

The first two types of intervention suffer from a delay between observing the presence of infection and the effectiveness of the intervention caused by the time taken to distribute the vaccine or organise treatment. There may be a period after the vaccine or treatment have been administered before they become fully effective. The first type of intervention may be delayed by the time taken to identify and to trace the individuals that may have come into contact with the infected individual. The third type of intervention will also be difficult to apply instantly. For all three types of intervention it will take time to ascertain which individuals are infectious. They may be a wait for lab tests or cultures to determine whether a patient showing symptoms has the disease. In many diseases (particular influenza-like illnesses) an individual will become infectious before the onset of symptoms and therefore will not be observed until well into (or after) their infectious period. Finally, a delay can be caused by patients not reporting symptoms straight away.

There is some variation between papers concerning the amount of time between an individual's infectious period and the time at which an intervention is ap-

plied. Not all papers explicitly include delay and very few incorporate a delay of random length. Müller *et al.* (2000) consider a branching process model with contact tracing, in which the whole population is periodically screened. This model has no delay between the time at which an individual is identified as infectious and the end of not only their own infectious period but also the end of the infectious periods of all of their successfully identified contacts. If this model included a delay before the intervention is applied to the index case or their contacts then fewer cases would be identified during their infectious period and therefore the epidemic would be more severe. Ball *et al.* (2007) implement a vaccination and isolation based intervention at the end of the infectious period of the first individual to be diagnosed, and therefore no delay is included in the model. Becker *et al.* (2005) study a stochastic epidemic model with constant latent and infectious periods. Individuals are diagnosed a constant time after their infection, at which point various interventions are considered. The time before diagnosis can be thought of as including the time necessary for the intervention to become effective, and therefore this model can include a delay before intervention. Kaplan *et al.* (2002) use a deterministic epidemic model to assess the effectiveness of a contact tracing based control measure in response to a bioterrorist smallpox attack. Although their model does not explicitly feature a delay between identifying an infectious individual and the end of their infectious period, newly identified contacts are put into a queue for vaccination and therefore this model incorporates a delay before the vaccine is applied. Varying the length of this delay is not explored.

Longini *et al.* (2004) use a discrete time stochastic model with a fixed delay before the intervention to model the effectiveness of antiviral prophylaxis at

containing a new influenza strain. They find that increasing the delay before the intervention rapidly reduces its effectiveness. When the delay is more than 3 days (when the incubation period has mean 1.9 days) the intervention is no longer sufficient to contain the outbreak.

Eubank *et al.* (2004) simulate an epidemic on a dynamic bipartite graph designed to capture the contact structure of a population realistically. They include a delay before intervention and allow infected individuals to withdraw to the home. They find that the time taken for infected individuals to withdraw to the home and the delay before intervention have a much greater effect on the outcome of the epidemic than the vaccination strategy. This highlights how important these delay parameters are on the model, and therefore they should be chosen with care.

The principal focus of this chapter is to calculate the threshold parameter for a continuous time epidemic model that includes a delay between diagnosis and intervention. Two probability distributions for the length of this delay are considered: the exponential distribution and the constant distribution. In section 3.3, methods are derived to find the threshold parameter for a model with exponentially distributed delays, but no latent period. Exponentially distributed latent periods are then added to this model and the threshold parameter recalculated in section 3.4. The next two sections, section 3.5 and section 3.6 explore the model with constant delay length, first without and then with exponentially distributed latent periods. In sections 3.7 and 3.8, a branching process version of the model is considered, firstly with exponentially distributed delays and then with constant delays. The penultimate section draws a comparison between the two delay period distributions. Finally section 3.10 of this chapter

outlines a method to find the threshold parameter for discrete time epidemic models that feature an intervention.

3.2 Definition of the Model

Consider a fixed population of N individuals divided into equal sized households. At any point in time, each individual can be in one of five categories: susceptible, latent, infective, removed or response. Any two individuals in the population come into contact at times given by the points of a homogeneous Poisson process with rate λ/N. Individuals that are in the same household make additional contacts at the points of a homogeneous Poisson process with rate β. Any such contact between a susceptible and an infective results in the immediate infection of the susceptible, who enters the latent category. Upon entering the latent category, an individual is allocated a latent period distributed according to the random variable T_E. During this period the individual has contracted the disease but is unable to infect other individuals. At the end of their latent period, an individual automatically enters the infective category. Infectives are able to infect susceptibles during their infectious period, which is distributed according to the random variable T_I. Once their infectious period is over, individuals enter the removed category where they remain for their removed period, which is distributed according to the random variable T_R. Finally, at the end of their removed periods, individuals enter the response category, in which they subsequently remain.

Denote the number of susceptible, latent, infective, removed and response individuals in a household at time t by the random variables $S(t)$, $E(t)$, $I(t)$, $R(t)$ and $V(t)$ respectively. The random vector $\boldsymbol{X}(t) = (S(t), E(t), I(t), R(t))$ fully represents the state of a household at time t since the household sizes are fixed, and therefore $V(t)$ can be deduced from $\boldsymbol{X}(t)$. If the household initially satisfies $S(0) = n$, $I(0) = i$ and $E(0) = R(0) = V(0) = 0$ then the state space of the

epidemic, denoted by Ω, is the set given by vectors of the form $(a, b, c, d) \in \mathbb{N}^4$ where

$$\begin{aligned} 0 &\leq a \leq n, \\ 0 &\leq b \leq n - a, \\ 0 &\leq c \leq n + i - a - b, \\ 0 &\leq d \leq n + i - a - b - c. \end{aligned}$$

The reproduction number for an epidemic model is a function of the parameters that gives an indication of the character of the epidemic that is likely to be produced. The basic reproduction number is defined as the expected number of individuals infected by a 'typical' infectious individual during the early stages of the epidemic, and therefore if the reproduction number is smaller than one the epidemic will die out, larger than one and a large epidemic becomes more likely.

For this households model the reproduction number is denoted by R_*, and is derived by considering a single household containing one infective together with a large number of entirely susceptible households. The infectious individual instigates a subepidemic within their own household and this epidemic will go on to cause further infections in other households. The parameter R_* is the expected number of these infections in other households. Since the number of households is assumed large, the possibility of infecting more than one individual in a household is ignored. Also, the probability of a global contact occurring between two individuals within the initial household is assumed to be zero. Therefore R_* is the rate at which global contacts are made (λ) multiplied by the expected sum of all the infectious periods created within the initial household. This sum is called the severity generated by a household and is

equal to $\int_0^\infty I(u)\,\mathrm{d}u$. Thus, if the households are all of size $n+1$,

$$R_* = \lambda \mathrm{E}\left[\int_0^\infty I(u)\,\mathrm{d}u \middle| \boldsymbol{X}(0) = (n, 0, 1, 0)\right].$$

A strong motivation to study epidemic models is to assess and compare the effectiveness of proposed control measures. In order to incorporate an intervention into the epidemic model, define the stopping time

$$T_v = \inf\{t \geq 0 : V(t) = v\}$$

where $v \in \mathbb{N}$ is called the intervention trigger. When the number of individuals in the response category reaches the intervention trigger it is assumed that the household is no longer able to make global contacts. This implies that after time T_v, any remaining infectious periods do not contribute to the global epidemic, and so R_* is reduced. Define $A(t) = \int_0^t I(u)\,\mathrm{d}u$ to be the severity up to time t generated by a household and call $A(T_v)$ the household's effective severity. The basic reproduction number R_* is therefore reduced to $\lambda \mathrm{E}[A(T_v)]$. Since λ is a parameter of the model, the aim of this research is to discover the expected effective severity (and therefore R_*) so define $\chi = \mathrm{E}[A(T_v)]$.

The intervention time is defined in the manner described above in order to be most flexible. The removed period may in fact comprise many different steps (a period before the individual's symptoms begin, the time needed to perform tests to identify the strain or the time needed to contact all of the household and distribute a vaccine) and so the first individual to enter the removed category need not be the same as the one to trigger the intervention. Also, the precise form of the intervention applied to the household has not been

assumed. For instance, a vaccine may be applied to prevent the susceptibles in the household from becoming infected, antiviral prophylaxis may be used to render the household immune and not infectious to the disease or most directly, the household may be isolated from the community until their infectious periods have passed. In reality, a combination of these measures could be imposed in order to prevent the household from making further external infections.

Although the expected severity is vital in determining the reproduction number, it may also be interpreted as the 'cost' of the epidemic as it contains information about the number of infections and the duration of the epidemic, and is therefore interesting in its own right, see Gani and Jerwood (1972).

3.3 Exponential infectious and removed periods without latent periods

This section considers the case in which the time spent in the removed category, T_R, has an exponential distribution. Initially it is assumed for simplicity that the latent period (the time between an individual's infection and the time at which they are able to infect other individuals) has zero length. This simplifies the derivations and allows a better understanding of the ideas involved before latent periods are added in section 3.4. The state of the epidemic at time t can now be represented by a vector $\boldsymbol{X}(t) = (S(t), I(t), R(t)) = (a, b, c) \in \mathbb{N}^3$ that satisfies

$$\begin{aligned} 0 &\leq a \leq n, \\ 0 &\leq b \leq n + i - b, \\ 0 &\leq c \leq n + i - a - b. \end{aligned}$$

3.3.1 Derivation of the expected effective severity

If the infectious period distribution (T_I) and the removed period distribution (T_R) are both assumed to be exponential then the model has the Markov property, allowing the following method for calculating the expected severity.

Assume that $T_I \sim \text{Exp}(\gamma)$ and $T_R \sim \text{Exp}(\mu)$ (where $\text{Exp}(\theta)$ denotes an exponential distribution with mean θ^{-1}) and define

$$x_{a,b,c} = \text{E}\left[\int_0^{T_v} I(u)\,\text{d}u \middle| \boldsymbol{X}(0) = (a, b, c)\right]$$

to be the expected effective severity of the epidemic, given that the epidemic

starts in state $(a, b, c) \in \Omega$. Since the population size is fixed to be $n + i$, the number of individuals in the response category if $\boldsymbol{X}(t) = (a, b, c)$ is $n + i - a - b - c$. A recursive formula for $x_{a,b,c}$ is now derived by conditioning on the time and then type of the first event.

$$\begin{aligned} x_{a,b,c} &= \mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u \middle| \boldsymbol{X}(0) = (a,b,c)\right] \\ &= \mathrm{E}\left[\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u \middle| \text{first event occurs at } T, \boldsymbol{X}(0) = (a,b,c)\right]\right] \\ &= \mathrm{E}\left[bT \middle| \boldsymbol{X}(0) = (a,b,c)\right] + \mathrm{E}\left[\mathrm{E}\left[\int_T^{T_v} I(u)\,\mathrm{d}u \middle| T, \boldsymbol{X}(0) = (a,b,c)\right]\right] \\ &= \frac{b}{f(a,b,c)} + \frac{\beta ab}{f(a,b,c)} x_{a-1,b+1,c} + \frac{\gamma b}{f(a,b,c)} x_{a,b-1,c+1} + \frac{\mu c}{f(a,b,c)} x_{a,b,c-1} \end{aligned} \tag{3.1}$$

for $a, b, c \in \Omega$ with $f(a, b, c) = \beta ab + \gamma b + \mu c > 0$. Since the epidemic ends once there are no infectives, we have that $x_{a,0,c} = 0$. A second boundary condition is produced by noting that no contribution is made to the severity once there are v individuals in the response category and the intervention is applied. This gives $x_{a,b,c} = 0$ for $a+b+c \leq n+i-v$. Solving the three-dimensional recurrence relation (3.1) involves tracing every path from the start state to a boundary. Since no state can be visited by the epidemic twice and there are finitely many states, the paths are of finite length and there are finitely many of them. It is therefore possible to find the expected effective severity $\chi = x_{n,i,0}$ by applying recurrence relation (3.1) finitely many times.

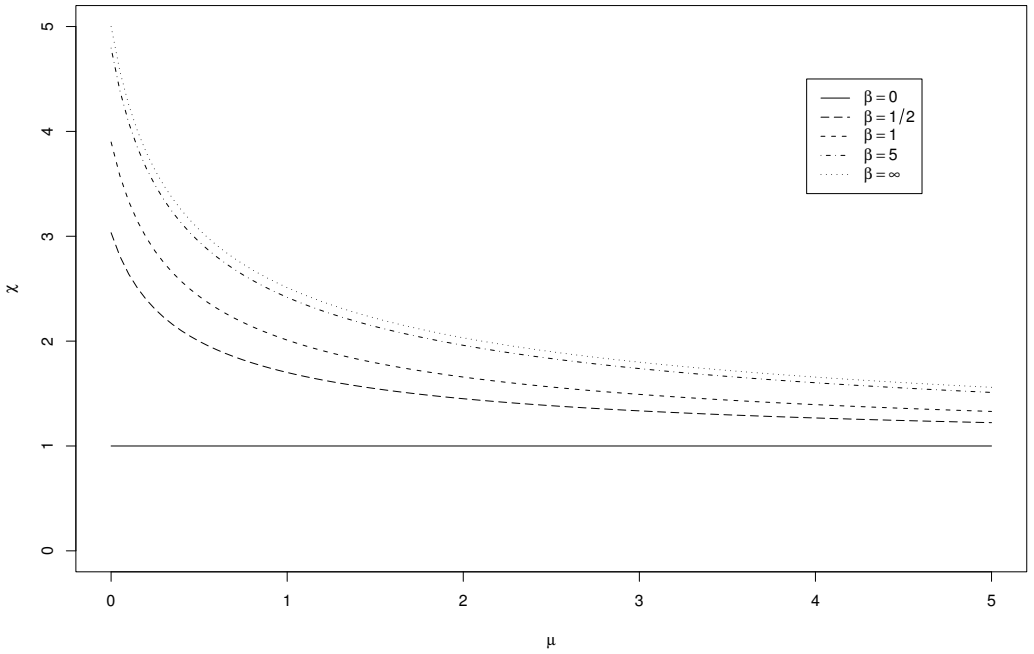

Figure 3.1: The expected effective severity χ against μ, with $n = 4$, $i = v = 1$ and $\gamma = 1$.

3.3.2 Effects of parameter changes

In this section the effects of changing the parameters on the expected effective severity (χ) are explored in three numerical examples in order to demonstrate quantitative results for plausible parameter values and to identify more general qualitative trends that have a practical significance. Although not included here, other parameter combinations have been explored and do not affect the general trends described below. Since there is a degree of freedom in the choice of one parameter, the infectious periods have been normalised to have a mean length of 1.

Figure 3.1 shows the effect on χ of increasing the response rate μ, the rate at which removed individuals are transferred into the response category. When μ

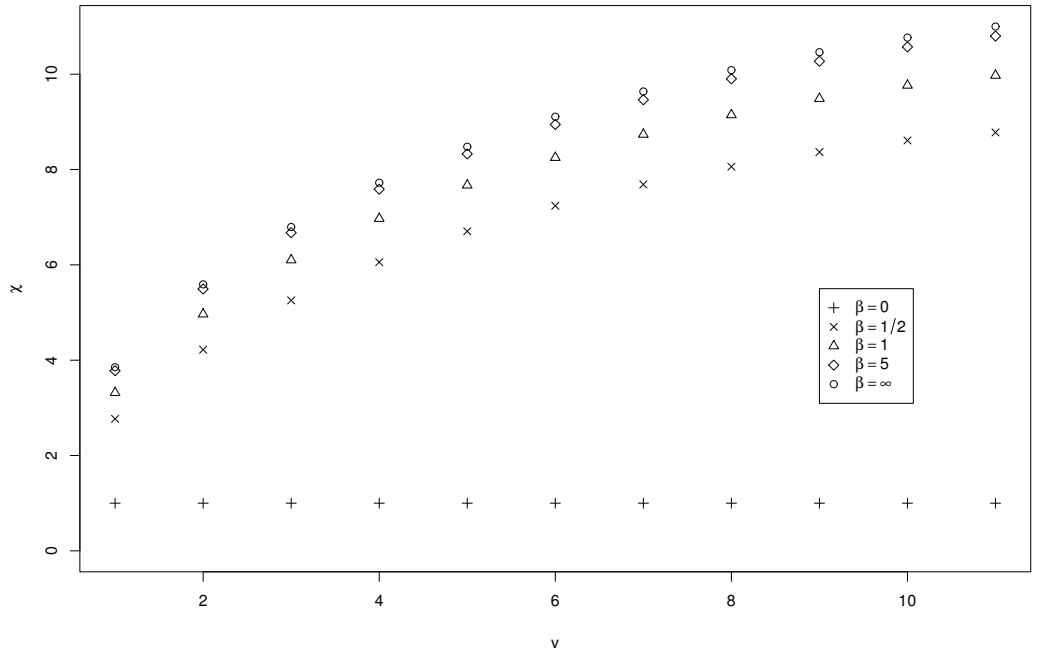

Figure 3.2: The expected effective severity χ against v, with $n = 10$, $i = 1$, and $\gamma = \mu = 1$.

is zero the intervention cannot occur and so the graph begins at the expected severity of the epidemic without intervention. Increasing μ raises the probability that the intervention will occur before the epidemic ends naturally. It also causes the intervention to occur earlier in the epidemic and therefore χ is a decreasing function of μ. As μ tends to infinity χ approaches the expected severity up to the vth *removal* which is v/γ (Watson, 1980), which is equal to one here. When no infections can occur ($\beta = 0$) the intervention has no effect on the epidemic and so for this case the severity is equal to the infectious period of the single initial infective and is therefore independent of μ. The most important thing to note about figure 3.1 is that χ drops very rapidly as μ is increased from zero. This implies that if the response rate is too small, the intervention will have very little effect. It also clearly demonstrates that

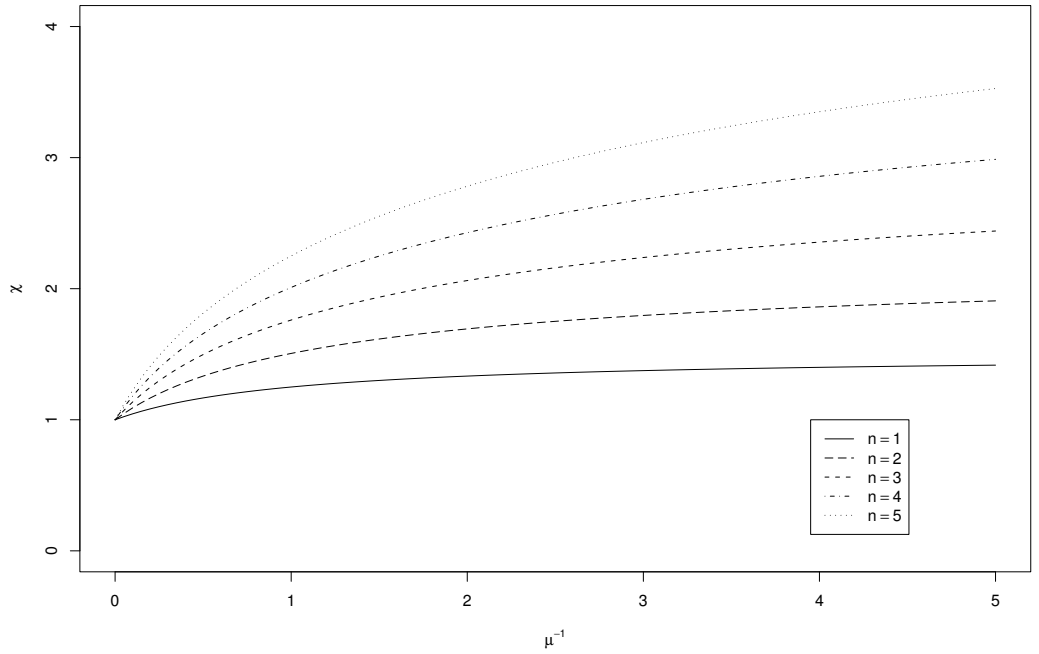

Figure 3.3: The expected effective severity χ against μ^{-1}, with $i = v = 1$ and $\beta = \gamma = 1$.

any delay in the intervention is detrimental to its effectiveness. It is also worth noting that the graphs for $\beta = 1$ and $\beta = 5$ are quite close to $\beta = \infty$, and so the degree of infectiousness of a disease does not have a large effect on χ here. This is very useful in practice as for an emerging disease the value of β will be unknown and difficult to estimate, and so the case in which β is infinite provides a useful upper bound on χ.

Figure 3.2, shows the effect of increasing the intervention trigger v on a large household of 11 individuals. Such a large household was chosen to allow a greater number of values of v to be explored. Obviously χ increases as v is increased, but for larger values, the increase is smaller. This is because a small value of v is likely to prevent the epidemic from getting off the ground whereas

a larger v merely truncates a developed epidemic. Also, changing the value of β has slightly more effect on the expected severity if v is larger, because longer outbreaks can occur if the intervention trigger is higher.

Finally, figure 3.3 demonstrates the effect on χ of increasing the household size, whilst keeping the intervention trigger constant at $v = 1$. The curves are plotted as functions of the expected removed period μ^{-1}. For larger values of n there are more individuals in the epidemic, and so more infectious individuals can be created before the intervention is applied. Thus, χ is strictly increasing in n. At first glance it appears that doubling the number of initial susceptibles doubles the height of χ above 1. However, a more careful study reveals that doubling the number of initial susceptibles more than doubles the height of the expected effective severity above 1. This stems from the potential of the new initial susceptibles to go on to infect the original susceptibles that would otherwise have avoided infection.

3.4 Exponential latent, infectious and removed periods

In section 3.3.1, the expected severity until the vth entry into the response category was found by using the Markov property to derive a recurrence relation. If the latent period distributions are not exponential, this method will no longer work. Conversely, the method continues to work if the latent periods are exponentially distributed, as the Markov property is preserved.

3.4.1 Derivation of the expected effective severity

Assume that the latent periods are exponentially distributed with mean length κ^{-1}. Closely following section 3.3.1, define for $(a, b, c, d) \in \Omega$,

$$x_{a,b,c,d} = \mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u \middle| \boldsymbol{X}(0) = (a, b, c, d)\right].$$

Since the initial state is now $\boldsymbol{X}(0) = (n, 0, i, 0)$, the number of individuals in the response category if $\boldsymbol{X}(t) = (a, b, c, d)$ is $n + i - a - b - c - d$. Using the same argument as in 3.3.1 we derive that

$$\begin{aligned} x_{a,b,c,d} \;=\; & \frac{c}{f(a,b,c,d)} + \frac{\beta ac}{f(a,b,c,d)} x_{a-1,b+1,c,d} + \frac{\kappa b}{f(a,b,c,d)} x_{a,b-1,c+1,d} \\ & + \frac{\gamma c}{f(a,b,c,d)} x_{a,b,c-1,d+1} + \frac{\mu d}{f(a,b,c,d)} x_{a,b,c,d-1} \end{aligned} \tag{3.2}$$

for $a, b, c, d \in \Omega$ with

$$f(a, b, c, d) = \beta ac + \kappa b + \gamma c + \mu d > 0.$$

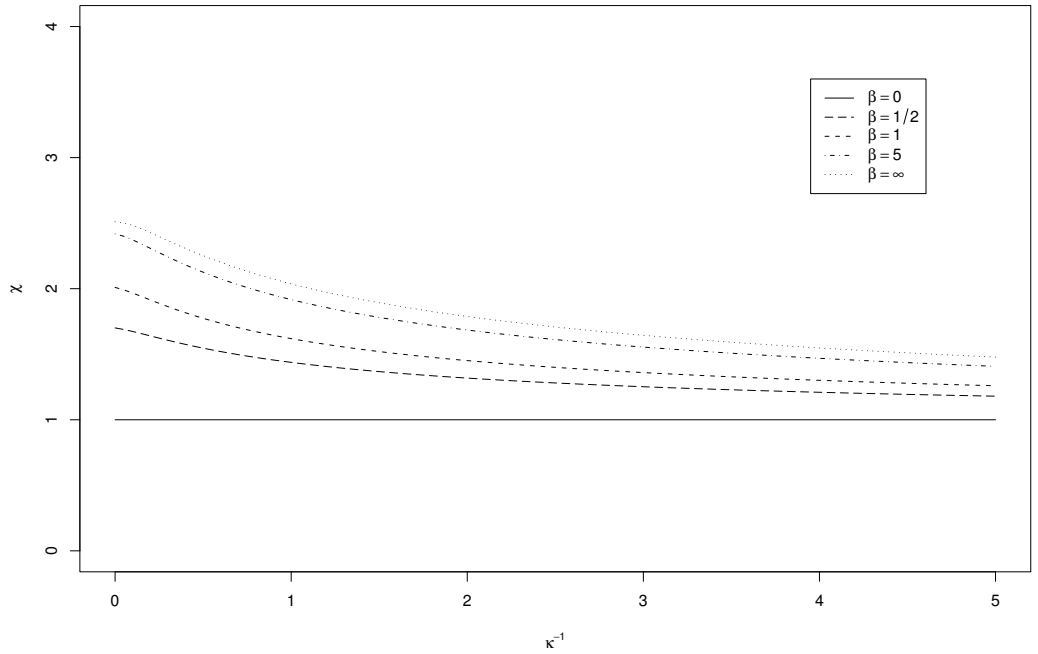

Figure 3.4: The expected effective severity χ against κ^{-1} with $n = 4$, $i = v = 1$ and $\gamma = \mu = 1$.

The boundary conditions are $x_{a,0,0,d} = 0$ for $a + d \leq n + i - v$ and $x_{a,b,c,d} = 0$ for $a + b + c + d \leq n + i - v$. Since the state space of the epidemic is finite and no state can be visited more than once, finitely many applications of equation (3.2) yield a solution for $\chi = x_{n,0,i,0}$.

3.4.2 Effects of parameter changes

Figure 3.4 demonstrates the effect of increasing the expected latent period κ^{-1} on the expected effective severity χ generated by an epidemic in a household of five individuals, one of whom is initially infectious. The intervention is set to occur when a single individual enters the response category. Clearly longer latent periods reduce χ, but notice that the graph is not very steep. This

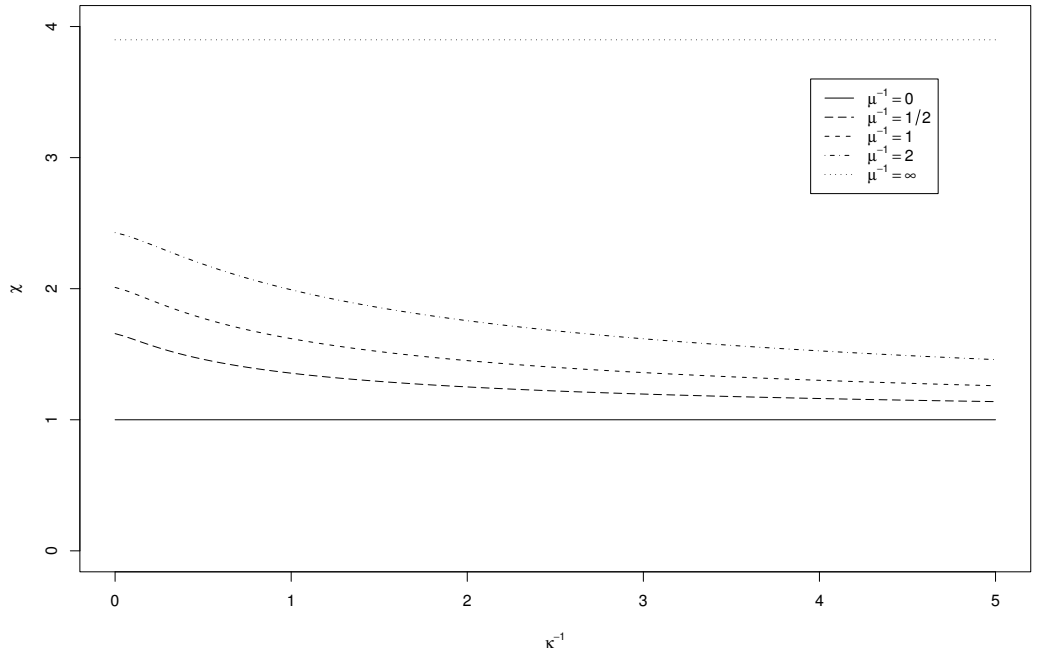

Figure 3.5: The expected effective severity χ against κ^{-1} with $n = 4$, $i = v = 1$ and $\gamma = \beta = 1$.

is because latent periods do not change the total severity generated by an epidemic without intervention. Instead they affect the model by spreading the severity over a longer time period and reducing the amount that occurs before the intervention. Also notice that χ is fairly robust to changes in the infection rate β. Although increasing β increases the expected severity, in this instance much of the extra severity would be generated after the intervention occurs, as $v = 1$.

Figure 3.5 is a variation on figure 3.4 with the expected removed period allowed to range over a set of values and the infection rate β fixed at one. Thus the curve for $\beta = \mu^{-1} = 1$ appears on both figures. This figure demonstrates the influence of the expected removed period on the expected effective severity χ when there

are latent periods. The expected latent period has a much smaller effect than the expected removed period because short removed periods can curtail a larger epidemic. Also notice that the latent period distribution has no effect on the expected severity when the removed periods are almost surely zero or infinite. Obviously infinite removed periods mean that the intervention cannot occur and so the latent periods don't affect the expected severity. However when the removed periods are almost surely zero, the intervention occurs at the time of the vth *removal*. The random time transform of Watson (1980) demonstrates that the expected severity until the vth removal is unchanged by the distribution of the latent periods, and this is verified by the graph.

3.5 Constant removed periods with exponential infectious periods and no latent period

When the period of time spent in the removed category has a constant length, the time between a case being observed and the intervention being applied to their household has a constant length. This kind of delay may occur if the patient is tested to confirm whether or not they have the disease in question or some other infection before the vaccine is applied. Measures like this may be introduced if there is a cost associated with vaccination (for instance a financial cost, a shortage of the vaccine or a risk of side-effects) and the number of vaccinations is required to be kept as small as possible. As with the exponential removed period, the methods used to find the expected effective severity χ are first described for the case without latent periods for simplicity.

Recall that,

$$T_v = \inf\{t \geq 0 : V(t) = v\}$$

and define

$$U_v = \inf\{t \geq 0 : R(t) + V(t) = v\}.$$

Notice that U_v is the time of the vth removal (as opposed to the vth individual to enter the response category) and so U_v is always less than T_v.

Under the assumption that the removed period is a constant of fixed length $T_R \equiv L$, then $T_v = U_v + L$. Thus,

$$\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u\right] = \mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] + \mathrm{E}\left[\int_{U_v}^{U_v+L} I(u)\,\mathrm{d}u\right]$$

$$\begin{aligned} &= \mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] \\ &\quad + \sum_{k=0}^{n+i-v} \mathrm{E}\left[\int_{U_v}^{U_v+L} I(u)\,\mathrm{d}u \Big| I(U_v)=k\right] \mathrm{P}(I(U_v)=k) \\ &= \mathrm{E}[A(U_v)] + \sum_{k=0}^{n+i-v} \mathrm{E}[A(L)|I(0)=k]\mathrm{P}(I(U_v)=k). \end{aligned}$$

Notice that since v individuals have been removed at time U_v, the information $I(U_v)=k$ implies that $S(U_v)=n+i-k-v$. In order to calculate the expected effective severity, we therefore need to evaluate (i) the expected severity up to the vth removal, $\mathrm{E}[A(U_v)]$; (ii) the distribution of the number of infectives just after the vth removal, $\mathrm{P}(I(U_v)=k)$; and (iii) the expected severity up to time L, $\mathrm{E}[A(L)|I(0)=k]$.

3.5.1 The expected severity up to the vth removal

There are two methods of finding the expected severity up to the vth removal. The first method uses a random time scale transform to find the expected severity conditional on the final size of the epidemic. The second method produces a recurrence relation that can be solved to find the expected severity.

The random time scale method

Watson (1980) introduces a useful random time-scale transformation that can be used to find the expected severity up to the vth removal of the Markov SIR epidemic model. Recall that

$$A(t) = \int_0^t I(u)\,\mathrm{d}u$$

is the severity generated by the epidemic until time t. This function is increasing until the number of infectious individuals reaches zero - call this (stopping) time Z, so that

$$Z = \inf\{t \geq 0 : I(t) = 0\}.$$

For $t \geq Z$, $A(t) = A(Z)$.

Form a new process $\{\boldsymbol{X}'(u) : 0 \leq u \leq A(Z)\}$ from $\{\boldsymbol{X}(t) : t \geq 0\}$ by running the clock k times slower in the new process, where k represents the number of infectives in the current state of the epidemic. For example, if the process $\{\boldsymbol{X}(t) : t \geq 0\}$ remains in the initial state $(n, i, 0)$ for 2 time units, the new process $\{\boldsymbol{X}'(u) : 0 \leq u \leq A(Z)\}$ remains in the initial state for $2i$ time units. Thus, the 'time' until a particular event in the new process corresponds to the severity that the epidemic generates until the same event occurs in the original process. So if an event occurs at time T in the original process, its corresponding event in the transformed process will occur at time $T' = A(T)$. This continues until the number of infectives in the epidemic reaches zero.

Thus, for $0 \leq t \leq Z$,

$$\boldsymbol{X}'(A(t)) = \boldsymbol{X}(t).$$

From this construction it is clear that when the process $\{\boldsymbol{X}'(u) : 0 \leq u \leq A(Z)\}$ is in state (x, y, z); infections occur at a rate βx and removals occur at a rate γ. Thus, the removals occur at the points of a homogeneous Poisson process with rate γ until the final removal at time $Z' = A(Z)$. This implies that the severity generated between removals has an exponential distribution with mean γ^{-1}, and so if v removals occur the expected severity up to the vth removal has

a gamma distribution with mean v/γ, c.f. Ball *et al.* (2007). Therefore,

$$\mathrm{E}[A(U_v)|v \text{ removals occur}] = \frac{v}{\gamma}.$$

If v is larger than i then v removals are not certain to occur as the epidemic may die out having infected insufficiently many individuals. In this case $U_v = \infty$ and so $U_v' = Z' = A(Z)$.

Summing over the final size distribution of the epidemic can be used to remove the condition that v removals are certain to occur, since if the final number of initially susceptible individuals infected is k, then $k+i$ removals are certain to occur.

$$\mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] = \sum_{k=0}^{n} \frac{\min\{k+i, v\}}{\gamma} \mathrm{P}(\text{Final Size } = k).$$

Notice that if $i \geq v$ this simplifies to

$$\mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] = \frac{v}{\gamma}$$

because v removals are certain to occur.

The recurrence relation method

Instead of calculating the final size distribution, in practice it is often easier to use the second method of finding the expected severity until the vth removal. This method adapts the recurrence relation approach used in section 3.3. Since all that is required is the expected severity until the vth removal, it is sufficient to keep track of only the first two categories of the epidemic: the susceptibles

and the infectives. Defining

$$x_{a,b} = \mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right],$$

then

$$x_{a,b} = \frac{1}{\beta a+\gamma} + \frac{\beta a}{\beta a+\gamma}x_{a-1,b+1} + \frac{\gamma}{\beta a+\gamma}x_{a,b-1}$$

for $a, b \in \mathbb{N}$ and with the boundary conditions

$$\begin{aligned} x_{a,0} &= 0 \text{ for } a \in \{0,1,\ldots,n\}, \\ x_{a,b} &= 0 \text{ for } a+b < n+i-v. \end{aligned}$$

The first two categories of the epidemic form a continuous time Markov process with a finite state space in which no state can be returned to once it has been visited and therefore a finite number of applications of this recurrence relation and its boundary conditions yield a solution for $x_{n,i}$.

3.5.2 The distribution of the number of infectives after the vth removal

Once an individual has entered the removed category or the response category they can no longer affect the susceptible or infective processes and therefore contribute to the model only through the intervention time. Thus, in order to find the distribution of the number of infectives just after the vth removal, it is sufficient to keep track of the numbers of susceptible and infective individuals. Since this pair is a Markov process, the times between events can be ignored and the embedded discrete time process used to find the required distribution.

The state of this process after the vth removal is characterised by the number of infectives, because if the number of infectives is known to be k then the number of susceptibles must be $n + i - v - k$. If the number of susceptibles is larger than n (or less than 0) then obviously the probability of arriving in this state is zero. Thus, we require

$$\mathrm{P}(I(U_v) = k) = p_k$$

for $\max\{0, i - v\} \leq k \leq n + i - v$. There are two methods of calculating the p_k with different computational advantages and disadvantages, discussed later.

The matrix method

The distribution of the number of infectives just after the vth removal can be found by utilising matrices. Consider the embedded two dimensional discrete time Markov chain given by the states visited by the process

$$\{\boldsymbol{Y}(t) : t \geq 0\} = \{(S(t), I(t)) : t \geq 0\}.$$

The state space of this process (until v removals occur) is given by the set $\{(a, b) : 0 \leq a \leq n, i + n - a - v \leq b \leq i + n - a\}$. Define a matrix C by setting $c_{x,y}$ to be the probability that the embedded Markov chain goes to state y along a path containing only infections, except for the last jump which is a removal, given that the epidemic begins in state x. Obviously, many pairs of states cannot be connected by such a path, so the matrix will contain many zeros. In fact, from the state $(S(0), I(0)) = (a, b)$ $(b > 0)$ the epidemic can

reach precisely $a+1$ states, so for $k = 0, \ldots, a$,

$$c_{(a,b),(a-k,b+k-1)} = \frac{\gamma}{\beta(a-k)+\gamma} \prod_{l=0}^{k-1} \frac{\beta(a-l)}{\beta(a-l)+\gamma}$$

gives all the non-zero entries in the row corresponding to state (a, b).

If the epidemic process has an initial distribution given by the row vector $\boldsymbol{\alpha}$, then $\boldsymbol{\alpha}C$ gives the distribution of the epidemic after the first removal, from the definition of C. Iterating this argument implies that the distribution of the epidemic after the vth removal is given by $\boldsymbol{\alpha}C^v$. Thus, by pooling the states that have the same number of infectives, the distribution of the number of infectives after the vth removal is obtained.

The path evaluation method

A second method of calculating p_k, for $k = \max\{0, i-v\}, \ldots, n+i-v$ is produced by evaluating every possible path through the state space that the epidemic process can take. If a path has k infectives after the vth removal, add the probability of observing the path to p_k. However, if the path does not contain v removals (the epidemic dies out first) then the path can be ignored.

Figure 3.6 displays the structure of such an algorithm written in C. In this algorithm, the probability of observing a path without v removals (q) is also generated as a check, since

$$1 - q = \sum_{k=0}^{n+i-v} p_k.$$

The algorithm is recursive (it calls itself) and terminates with the array `p` (of

```
void calculatePaths(int a, int b, int removals, long double prob) {
  if (removals==v) {
    p[b]+=prob;
  } else if (b==0) {
    q+=prob;
  } else {
    //Calculate the path created by an infection.
    if (a>0) {
      calculatePaths(a-1,b+1,removals,prob*beta*a/(beta*a+gamma));
    }
    //Calculate the path created by a removal.
    calculatePaths(a,b-1,removals+1,prob*gamma/(beta*a+gamma));
  }
}
```

Figure 3.6: A simple recursive algorithm to calculate the p_k from the call `calculatePaths(n,i,0,1)`.

length $n+i-v+1$) filled with the p_k ($k = 0, \ldots n+i-v$).

A comparison of the methods

Both the path evaluation method and the matrix method are useful in different situations. If v is small (one or two for example), then even for quite large populations the number of possible paths remains relatively small and the path evaluation method is very fast. However, for larger values of v the number of paths rapidly increases as the population size increases and so the path evaluation method takes much longer to compute. The matrix evaluation method can be used for any value of v provided that the number of states in the epidemic is not too large. If the population size is 60 (with one initial infective), then there are 1890 states and more than 3.5 million matrix entries. However, since most of them are zero, this calculation can be performed in a few minutes. The number of states (represented by $(S(t), I(t))$) is equal to $n(n+2i+3)/2$ and so the number of matrix entries is given by the square of this number. It therefore seems reasonable to assume that the computation time increases approximately

according to a quartic in n. However, for very large state spaces, the amount of computer memory needed to store the non-zero matrix entries becomes too large, and the computation becomes less feasible.

3.5.3 The expected severity up to time L

All that remains is to calculate the expected severity from U_v to $T_v = U_v + L$ conditional on the number of infectives just after the vth removal. Since the number of infectives after the vth removal implies the number of susceptibles (and therefore the state of the SIR epidemic), this problem is equivalent to finding the expected severity generated by an SIR epidemic until time L. There are two methods of calculating the expected severity up to time L, a path evaluation method and a matrix method.

The path evaluation method

Ball and Clancy (1995) find the generating function for expected severity for Downton's carrier-borne epidemic model using the method of Kryscio (1975). Downton's carrier-borne epidemic model reduces to the Markov SIR epidemic model if no individuals are directly removed from the epidemic. Alternatively, the asymptomatic carriage epidemic model studied in chapter 2 reduces to the Markov SIR epidemic model when there are no carriers. From either of these sources it is possible to derive the function $h_{n,i}(x, y, \theta, t)$ defined and given below. Let $n, i \in \mathbb{N} \cup \{0\}$ then the state space of the SIR epidemic with n

initial susceptibles and i initial infectives is

$$\Omega_{n,i} = \{(x,y) \in \mathbb{Z}^2 : 0 \leq x \leq n, 0 \leq y \leq n+i-x\}.$$

For $(x,y) \in \Omega_{n,i}$ and $\theta, t \geq 0$,

$$\begin{aligned} h_{n,i}(x,y,\theta,t) &= \mathrm{E}\left[\exp\left(-\theta \int_0^t I(u)\,\mathrm{d}u\right) \mathbb{1}_{\{(S(t),I(t))=(x,y)\}} \middle| (S(0),I(0)) = (n,i)\right] \\ &= \sum_{(u,w)\in E} C_1(u,w|n,i) C_2(u,w|x,y) \exp(-t(\beta uw + (\gamma+\theta)w)) \end{aligned}$$

where

$$\begin{aligned} C_1(u,w|n,i) &= \sum_{d\in D_1} \prod_{k=0}^{L_1-1} \frac{a_k}{b_k + \theta s_{k,2} - b_{L_1} - \theta s_{L_1,2}}, \\ C_2(u,w|x,y) &= \sum_{d\in D_2} \prod_{k=0}^{L_2-1} \frac{a_k}{b_{k+1} + \theta s_{k+1,2} - b_0 - \theta s_{0,2}} \end{aligned}$$

and $E \subseteq \Omega_{n,i}$ is the set of states (u,w) that it is possible to pass through on a path from (n,i) to (x,y). The set D_1 contains all possible paths from (n,i) to (u,w) (they have length $L_1 = 2(n-u)+i-w$) and the set D_2 contains all possible paths from (u,w) to (x,y) (they have length $L_2 = 2(u-x)+w-y$). The state $(s_{k,1}, s_{k,2}) \in E$ denotes the state of the epidemic $(S(t), I(t))$ after $0 \leq k \leq l$ steps along the path d with length l. Finally,

$$\begin{aligned} a_k &= \begin{cases} \beta s_{k,1} s_{k,2} & \text{if } s_{k+1,2} = s_{k,2} + 1 \\ \gamma s_{k,2} & \text{if } s_{k+1,2} = s_{k,2} - 1 \end{cases} \\ b_k &= \beta s_{k,1} s_{k,2} + \gamma s_{k,2}. \end{aligned}$$

In order to find the required expected severity between time $t = 0$ and time $t = L$ note that

$$\mathrm{E}\left[\int_0^L I(u)\,\mathrm{d}u \Big| (S(0), I(0)) = (n, i)\right] = -\sum_{x=0}^{n}\sum_{y=0}^{n-x}\left[\frac{\mathrm{d}}{\mathrm{d}\theta}h_{n,i}(x, y, \theta, L)\right]_{\theta=0}. \quad (3.3)$$

Calculation of the derivative in equation (3.3) is straightforward and we obtain

$$\frac{\mathrm{d}}{\mathrm{d}\theta}h_{n,i}(x, y, \theta, t) = \sum_{(u,w)\in E}\exp(-t(\beta uw + (\gamma+\theta)w))\Big[C_1'(u, w|n, i)C_2(u, w|x, y) + C_1(u, w|n, i)C_2'(u, w|x, y) - twC_1(u, w|n, i)C_2(u, w|x, y)\Big]$$

where

$$\begin{aligned} C_1'(u, w|n, i) &= \sum_{d\in D_1}\left(\prod_{k=0}^{L_1-1}\frac{a_k}{b_k + \theta s_{k,2} - b_{L_1} - \theta s_{L_1,2}}\right) \\ &\quad \times \left(\sum_{j=0}^{L_1-1}\frac{s_{j,2} - s_{L_1,2}}{b_j + \theta s_{j,2} - b_{L_1} - \theta s_{L_1,2}}\right), \\ C_2'(u, w|x, y) &= \sum_{d\in D_2}\left(\prod_{k=0}^{L_2-1}\frac{a_k}{b_{k+1} + \theta s_{k+1,2} - b_0 - \theta s_{0,2}}\right) \\ &\quad \times \left(\sum_{j=0}^{L_2-1}\frac{s_{j+1,2} - s_{0,2}}{b_{j+1} + \theta s_{j+1,2} - b_0 - \theta s_{0,2}}\right). \end{aligned}$$

However, numerical evaluation of equation (3.3) is complicated by the large number of terms that need to be added together - particularly problematic for small values of L where the rounding errors may dominate.

The matrix method

A second method of obtaining the expected severity between the vth removal and the intervention is possible using the generator matrix. Let $X(t)$ represent the state of a continuous time Markov process at time t, let $\mathcal{F}(t)$ represent the σ-field generated by the process up to time t, let Q be the generator matrix of the process (with (i,j)th entry $q_{i,j}$), let s be a function from the state space Ω to $\mathbb{R}$ and for $i, j \in \Omega$ define

$$r_{i,j}(\theta, t) = \mathrm{E}\left[e^{-\theta \int_0^t s(X(u))\,\mathrm{d}u} \mathbb{1}_{\{X(t)=j\}} \middle| X(0) = i\right].$$

For $\Delta t > 0$,

$$\begin{aligned} & r_{i,j}(\theta, t+\Delta t) \\ &= \mathrm{E}\left[\mathrm{E}\left[e^{-\theta \int_0^t s(X(u))\,\mathrm{d}u} e^{-\theta \int_t^{t+\Delta t} s(X(u))\,\mathrm{d}u} \mathbb{1}_{\{X(t+\Delta t)=j\}} \middle| \mathcal{F}(t)\right] \middle| X(0) = i\right]. \end{aligned}$$

Next, recall that as $x \to 0$, $\exp(x) = 1 + x + o(x)$ and $\int_t^{t+x} f(u)\mathrm{d}u = f(t)x + o(x)$ (for measurable f). Thus,

$$\begin{aligned} & r_{i,j}(\theta, t+\Delta t) \\ &= \mathrm{E}\left[e^{-\theta \int_0^t s(X(u))\,\mathrm{d}u} \mathrm{E}\left[(1 - \theta \Delta t s(X(t)) + o(\Delta t)) \mathbb{1}_{\{X(t+\Delta t)=j\}} \middle| \mathcal{F}(t)\right] \middle| X(0) = i\right]. \end{aligned}$$

Now,

$$\begin{aligned} \mathrm{E}\left[\mathbb{1}_{\{X(t+\Delta t)=j\}} \middle| \mathcal{F}(t)\right] &= \sum_{k \neq j} \mathbb{1}_{\{X(t)=k\}} \Delta t q_{k,j} + \mathbb{1}_{\{X(t)=j\}}(1 + \Delta t q_{j,j}) + o(\Delta t) \\ &= \sum_{k} \mathbb{1}_{\{X(t)=k\}} (\Delta t q_{k,j} + \delta_{k,j}) + o(\Delta t) \end{aligned}$$

so

$$\begin{aligned} & r_{i,j}(\theta, t+\Delta t) \\ &= \sum_k \mathrm{E}\left[e^{-\theta\int_0^t s(X(u))\,\mathrm{d}u}(\Delta t q_{k,j} + \delta_{k,j}(1-\theta\Delta t s(X(t))))\mathbb{1}_{\{X(t)=k\}}\middle| X(0)=i\right] \\ &\quad + o(\Delta t) \\ &= (1-\theta\Delta t s(j))r_{i,j}(\theta,t) + \sum_k \Delta t q_{k,j} r_{i,k}(\theta,t) + o(\Delta t), \end{aligned}$$

which implies that

$$\frac{\mathrm{d}r_{i,j}(\theta,t)}{\mathrm{d}t} = \sum_k r_{i,k}(\theta,t)q_{k,j} - \theta s(j) r_{i,j}(\theta,t). \tag{3.4}$$

Define

$$a_{i,j}(\theta) = \begin{cases} q_{i,j} & i \neq j \\ q_{j,j} - \theta s(j) & i = j \end{cases}$$

and

$$A(\theta) = [a_{i,j}(\theta)]_{i,j} \quad \text{and} \quad R(\theta,t) = [r_{i,j}(\theta,t)]_{i,j}.$$

Using this notation, equation (3.4) becomes

$$\frac{\partial R(\theta,t)}{\partial t} = R(\theta,t)A(\theta)$$

which has unique solution

$$R(\theta,t) = \exp(A(\theta)t).$$

This result for Markov reward processes with a finite state space is also proved in Ball *et al.* (1994). Differentiating this with respect to θ (see Appendix 2 of Ball and Sansom, 1989) yields

$$\frac{\partial R(\theta,t)}{\partial\theta} = \int_0^t e^{(t-u)A(\theta)}\frac{\partial A(\theta)}{\partial\theta}e^{uA(\theta)}\,\mathrm{d}u.$$

Next, substituting $\theta = 0$ gives

$$\left.\frac{\partial R(\theta,t)}{\partial\theta}\right|_{\theta=0} = \int_0^t e^{(t-u)Q}De^{uQ}\,\mathrm{d}u.$$

where D is a diagonal matrix with $d_{j,j} = s(j)$. This integral can be evaluated numerically.

Returning to the context of epidemics, let $\boldsymbol{\alpha}(x,y)$ represent the row vector of zeros with a single one in the row corresponding to the state (x,y); let $\mathbf{1}$ be a column vector of ones (with length equal to the size of the state space, $(n+1)(n+2i+2)/2$) and let D be a diagonal matrix with $d_{(x,y),(x,y)} = y$ (the number of infectives in the state), then,

$$\mathrm{E}\left[\int_0^L I(u)\,\mathrm{d}u\Big|S(0)=n, I(0)=i\right] = \int_0^L \boldsymbol{\alpha}(n,i)e^{(L-u)Q}De^{uQ}\mathbf{1}\,\mathrm{d}u.$$

A comparison of the methods

The path evaluation method for finding the expected severity of a Markov SIR epidemic up to time L (the first one described above) is very fast for small values of v as the number of possible paths remains small. However, as the number of paths gets larger, the number of terms to be added together becomes enormous

and so the number of rounding errors is very high. This can make the results produced inaccurate and unrealistic (decreasing in L for example), particularly for small values of L when the errors dominate. This suggests that the matrix method is more useful for $v > 2$, despite the need to use numerical methods to calculate the matrix exponentials and the integral. However, when the size of the state space is large, taking the exponential of the generator matrix may take a long time and large amounts of computer memory.

It is possible to transform the result for the matrix method into the result for the path evaluation method using the spectral representation of the matrix Q, see for example Wedderburn (1934). For example, from section 3.3.1 of Ball *et al.* (1994), we see that if the $n \times n$ matrix Q has n distinct eigenvalues $\lambda_1, \ldots, \lambda_n$ then there exist n matrices $E_1, \ldots, E_n$ such that

1. $Q = \sum_{i=1}^{n} \lambda_i E_i$,
2. $E_i E_j = \begin{cases} E_i & i = j, \\ 0 & i \neq j, \end{cases}$
3. $\sum_{i=1}^{n} E_i = I_n$.

Thus, $e^{tQ} = \sum_{i=1}^{n} e^{t\lambda_i} E_i$ and so

$$\begin{aligned} \int_0^t e^{(t-u)Q} D e^{uQ} \mathrm{d}u &= \sum_{i=1}^{n} \sum_{j=1}^{n} E_i D E_j \int_0^t e^{(t-u)\lambda_i + u\lambda_j} \, \mathrm{d}u \\ &= \sum_{i=1}^{n} \sum_{j=1}^{n} F_{i,j}(t) \end{aligned}$$

where

$$F_{i,j}(t) = \begin{cases} t e^{t\lambda_i} E_i D E_i & i = j, \\ \frac{e^{(\lambda_j - \lambda_i)t}}{\lambda_j - \lambda_i} E_i D E_j & i \neq j. \end{cases}$$

The terms of this matrix are a finite sum of terms proportional to e^{ct} and te^{ct} and therefore so is the expected severity found using the matrix method. The expected severity between 0 and L found using the path evaluation method is also a finite sum of terms with these two forms. Since these two methods must agree for every value of t, both the coefficients and the exponents in each term of the sums must agree. This demonstrates that although the methods appear to be very different, they do relate to one another, and identifies exactly how. It also suggests that the matrix method is slightly more general than the path evaluation method, as it does not require the assumption that the eigenvalues are all distinct.

3.5.4 Effects of parameter changes

The following figures were calculated using the recurrence relation method to find the expected severity until the vth removal (for simplicity) and the matrix methods for the other two parts, for flexibility and so that the value of v could be increased above two. Some calculations were repeated using the alternative methods to ensure that the results agreed.

Figure 3.7 displays the effect of increasing L, the constant time spent as a removed individual, on the expected effective severity χ. Increasing L strongly increases χ initially, but once L is above two or three, the intervention begins to have little effect, and so χ tends to the expected severity for the household without intervention. As β is increased χ strictly increases, however increasing β from one to infinity has remarkably little effect on χ. The similarity between five and infinity is particularly marked. This is because for these values of β it is likely that most of the household will be infected, and the times at

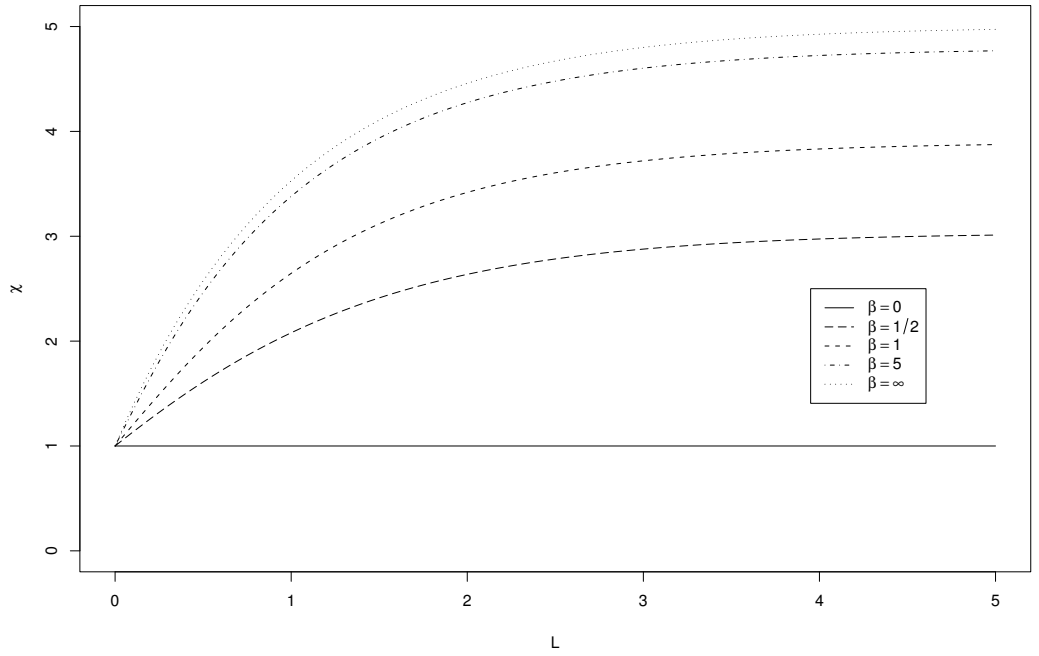

Figure 3.7: The expected effective severity χ against L with $n = 4$, $i = v = 1$ and $\gamma = 1$.

which they become infected are rendered largely unimportant by the period of time separating infection and response ($T_I + T_R$). During a real epidemic, the parameter β is unlikely to be known with any certainty and so this property of χ suggests that the case $\beta = \infty$ provides a useful upper bound.

Figure 3.8 shows the effect of increasing the intervention trigger v on the expected effective severity χ on a large household of ten individuals, one of whom is initially infectious. As v is increased, χ increases by an almost uniform amount until (when v is 10) no intervention can occur before the end of the epidemic. Again, β appears to have only a small effect on χ for the same reasons as for figure 3.7.

If the removed period L is increased to two (twice the expected infectious

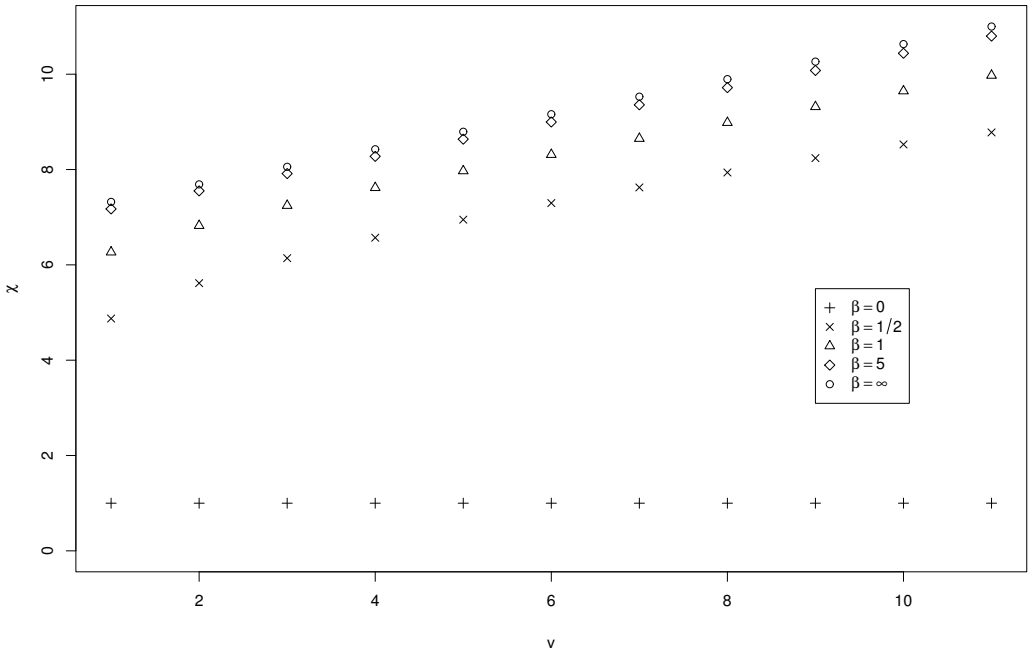

Figure 3.8: The expected effective severity χ against v with $n = 10$, $i = 1$ and $\gamma = L = 1$.

period) in figure 3.8 the graphs become much flatter, but still progress towards the same final point (at which no intervention occurs). Consequently for small v, χ is much larger. This is because a longer removed period allows the epidemic to progress much further and the intervention has little effect. Thus, changing the intervention trigger v has less effect on χ. Conversely, if the removed period is reduced to below the expected infectious period the intervention may be triggered earlier for small v, and so the graphs progress more steeply towards the same endpoint.

Figure 3.9 shows the effect of altering the number of initial susceptibles in a household on χ, against the removed period L. Obviously χ increases in n, but also notice that adding two susceptibles causes more than twice the increase of

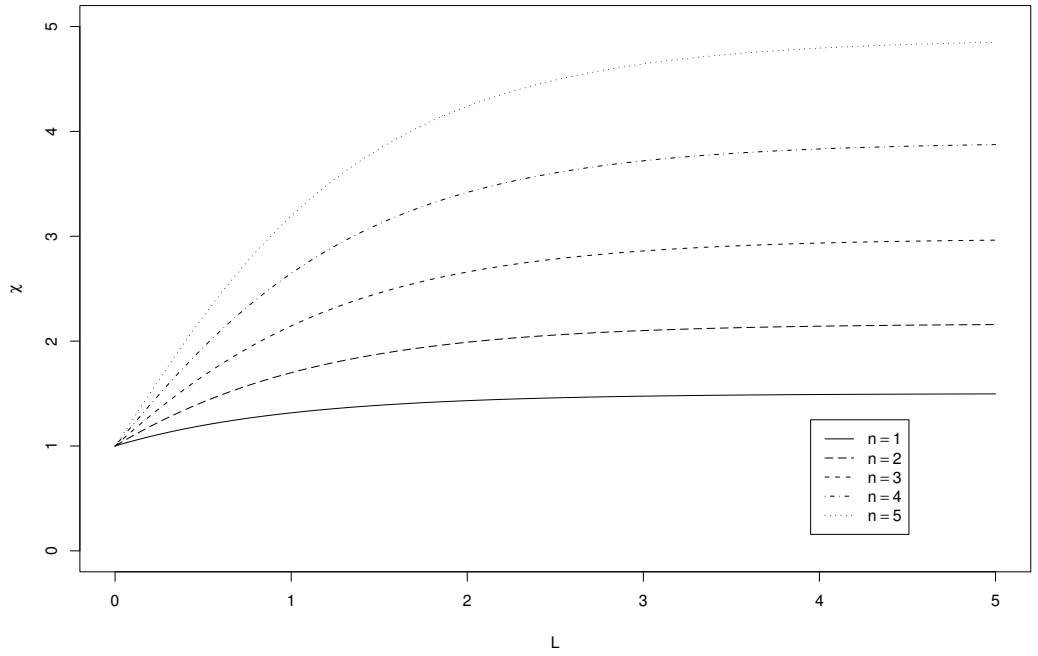

Figure 3.9: The expected effective severity χ against L with $i = 1$ and $\beta = \gamma = 1$.

adding one susceptible. This is because not only do the new susceptibles provide additional severity themselves, but they also add the potential to infect some of the existing susceptibles that would otherwise have avoided infection. Because of this, moving the intervention later (by increasing the removed period) has a larger effect on χ in the larger households, where the epidemic will take longer. This implies that if the household sizes are small, then an early intervention is vital if it is to have any substantial effect. In the larger households an earlier intervention still has a much stronger effect than a later one, however late interventions may still cause a worthwhile reduction in the expected effective severity.

3.6 Constant removed periods with exponential infectious and latent periods

The methods needed to find the expected effective severity for the constant removed period case rely upon the Markov property. Specifically, the Markov property needs to hold for the process $\{(S(t), E(t), I(t)) : t \geq 0\}$. For these methods to continue to work, it is therefore necessary for the latent periods to have an exponential distribution.

Section 3.5 decomposes the expected effective severity for the epidemic with constant removed periods and no latent periods. This decomposition is still possible after the addition of exponentially distributed latent periods, however, two of the three components become more complicated. Recall that

$$U_v = \inf\{t \geq 0 : R(t) + V(t) = v\}$$

and

$$T_v = \inf\{t \geq 0 : V(t) = v\} = U_v + L$$

where L is the length of the removed period.

Using these stopping times, the expected effective severity χ can be written as follows.

$$\begin{aligned} \chi &= \mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u\right] \\ &= \mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] + \mathrm{E}\left[\int_{U_v}^{U_v+L} I(u)\,\mathrm{d}u\right] \end{aligned}$$

$$
\begin{aligned}
&= \mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] \\
&\quad + \sum_{k=0}^{n+i-v}\sum_{l=0}^{k} \mathrm{E}\left[\int_{U_v}^{U_v+L} I(u)\,\mathrm{d}u \middle| (E(U_v), I(U_v)) = (l, k-l)\right] \\
&\qquad\qquad \times \mathrm{P}((E(U_v), I(U_v)) = (l, k-l))
\end{aligned}
$$

Since precisely v individuals have been removed at time U_v, the event $\{(E(U_v), I(U_v)) = (l, k-l)\}$ implies that $S(U_v) = n + i - k - v$.

3.6.1 The expected severity up to the vth removal

The random time-scale transform of Watson (1980) can be used to show that the expected severity until the vth removal is unchanged under the addition of a latent period. It is therefore sufficient to modify only the last two parts of the decomposition of the expected effective severity to incorporate exponentially distributed latent periods.

The argument runs as follows. Recall from section 3.5.1 that events at time T in the process $\{\boldsymbol{X}(t) : t \geq 0\}$ occur at time $T' = A(T)$ in the transformed process $\{\boldsymbol{X}'(u) : 0 \leq u \leq Z\}$, where $A(t) = \int_0^t I(u)\,\mathrm{d}u$. However, the latent periods in the process $\{\boldsymbol{X}(t) : t \geq 0\}$ do not contribute anything to the transformed process, and therefore the transformed process is independent of the distribution of the latent period as long as it is almost surely finite. Thus, the time between removals in the transformed process remains exponentially distributed with mean γ^{-1} and so the expected severity until the vth removal has a gamma distribution with mean v/γ.

Since the expected severity until the vth removal is independent of the latent period distribution, this might suggest that the expected severity until the vth entry into the response category is also independent of the latent period distribution, however this is not the case. Consider a household of two individuals called S and I. Assume that S is initially susceptible and I is an infective. If S is infected and ends their latent period before the removal of I then the expected severity will not depend upon the distribution of the latent period, because removals now occur twice as fast but severity is generated at twice the rate. However, if I is removed before the end of the latent period of S, then the amount of severity generated by S before I enters the response category clearly depends upon the latent period distribution. Consequently (if the intervention has any effect) the expected severity until the vth entry into the response category will be smaller for the model which includes latent periods than for the model without them. This implies that unlike the expected severity until the vth removal, the expected severity until the vth entry into the response category *is* reduced by the addition of latent periods.

3.6.2 The distribution of the number of infectives after the vth removal

Of the two methods given in section 3.5.2, the path evaluation algorithm is much easier to modify to incorporate latent periods. Firstly, it is necessary to keep track of the extra information of the number of latent individuals, and secondly the extra type of event (the end of a latent period) must be incorporated. These two modifications make the algorithm slightly more complex, but for realistic household sizes (up to six) the run-time of the algorithm remains almost

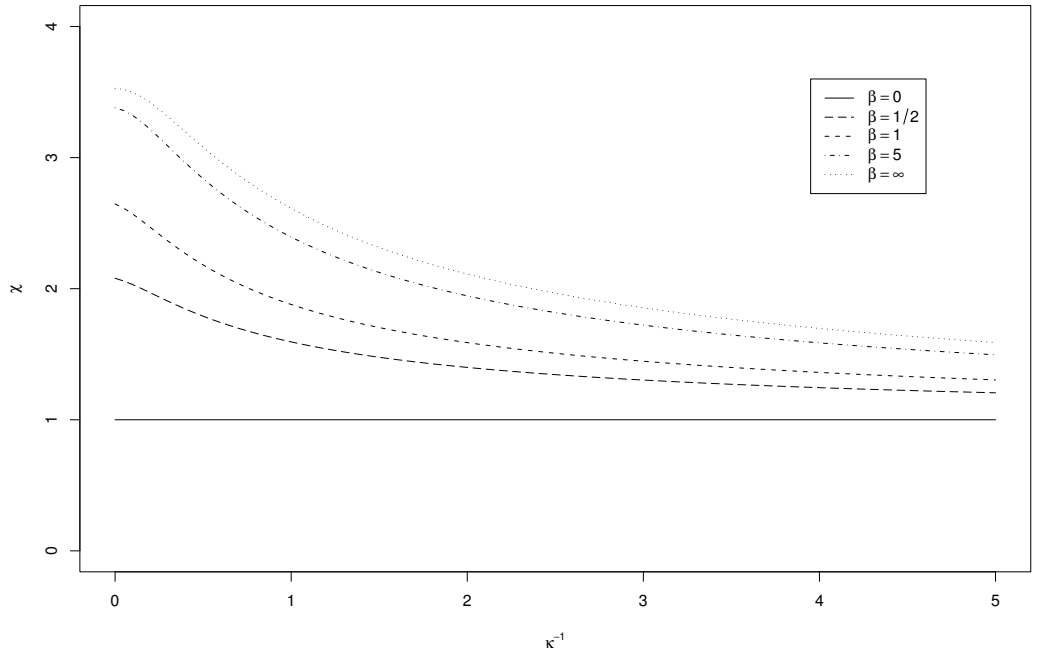

Figure 3.10: The expected effective severity χ against κ^{-1} with $n = 4$, $i = v = 1$ and $\gamma = L = 1$.

instantaneous. Modifying the matrix method is more difficult, as the entries of the matrix C ($c_{x,y}$ being the probability of the epidemic passing along a path from state x to state y, with the only removal occurring as the final step in the path) are now difficult to compute. This is because without latent periods there is only one kind of jump that is not a removal, but with them, there are now two kinds. The $c_{x,y}$ are sums over the order in which these events occur and therefore what was one term becomes complicated for households containing more than three or four individuals.

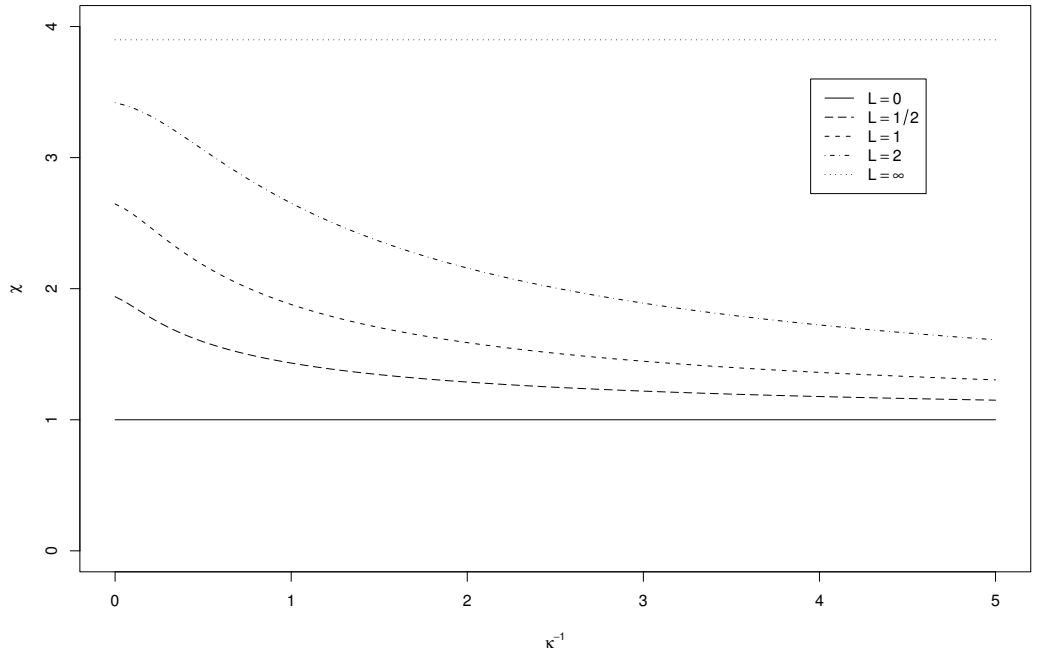

Figure 3.11: The expected effective severity χ against κ^{-1} with $n = 4$, $i = v = 1$ and $\gamma = \beta = 1$.

3.6.3 The expected severity up to time L

It is possible to modify both of the methods given in section 3.5.3 to find the expected severity generated by time L from a given starting state. The matrix method is simple to modify as it is a more general method, whereas the path evaluation method requires a large number of extra computations to be performed.

3.6.4 Effects of parameter changes

Figures 3.10 and 3.11 show the reduction in the expected effective severity χ as the expected latent period κ^{-1} is increased. On first glance, increasing

the expected latent period appears to have a stronger effect on χ in this case than in the exponential removed period case (figures 3.4 and 3.5). However, the proportional reduction in χ by adding latent periods is approximately the same, once the contribution of the initial infective (who does not undergo a latent period) has been ignored. Figure 3.10 also shows that as κ^{-1} is increased, the model becomes very robust to changes in β. This is because the other individuals are unlikely to reach the infective category before the intervention is triggered by the initial infective when the mean latent period is large. From figure 3.11 it is clear that the length of the latent period has no effect on χ when the intervention occurs at the vth removal ($L = 0$), as described by the argument in section 3.6.1.

3.7 Branching process approximation to the epidemic with exponential infectious and removed periods

We now consider the branching process approximation to an epidemic. This can be thought of as modelling an outbreak of infection caused by a finite number of initial infectives in an infinite, homogeneously mixing population of susceptible individuals. The branching process approximation is sometimes referred to as the initial approximation since it approximates the early stages of an epidemic in a finite (homogeneously mixing) population. This is the main motivation for studying it, as the approximation is unlikely to break down before the intervention has been applied. Note that since this model is not a households model, the intervention is now applied to every member of the population, representing a community wide intervention in real-life.

Consider a branching process in which an individual lives for a time T_I during which they give birth to new individuals at the points of a Poisson process with rate β. At the end of their lifetime individuals enter a removed category for time T_R before finally entering the response category. Define $I(t)$ to be the number of individuals alive (those capable of reproducing) at time t in the branching process, let $R(t)$ represent the number that are in their removed periods and let $V(t)$ be the number that have entered the response category. Let i be the number of initial ancestors, and assume that there are initially no individuals in the removed or response categories. From these definitions it is clear that new individuals are born at the points of a Poisson process with rate $\beta I(t)$. If T_I and T_R have exponential distributions with parameters γ and

μ respectively, then deaths occur at the points of a Poisson process with rate $\gamma I(t)$ and individuals enter the response category at the points of a Poisson process with rate $\mu R(t)$. Let $\boldsymbol{Y}(t) = (I(t), R(t), V(t))$ represent the state of the branching process at time t. Call the state space $\Omega \subseteq (\mathbb{N} \cup \{0\})^3$. The vector (a, b, c) is in Ω if $a + b + c \geq i$ and $c \leq v$.

As for the epidemic, define $A(t)$ to be the severity of the process up to time t,

$$A(t) = \int_0^t I(u)\,\mathrm{d}u$$

and let

$$T_v = \inf\{t \geq 0 : V(t) = v\},$$

then $\chi = \mathrm{E}[A(T_v)]$ is the expected effective severity - the expected severity up to the intervention. Note that since we are not (particularly) interested in the model with approximately infinite household sizes, finding the threshold parameter R_* is no longer our main motivation for finding χ. Instead, we simply use it as a measure of the cost of the epidemic.

3.7.1 Recurrence relation method

Using the same technique as for the epidemic model (section 3.3.1), it is possible to derive a recurrence relation for

$$y_{a,b,c} = \mathrm{E}[A(T_v)|\boldsymbol{Y}(0) = (a, b, c)]$$

specifically,

$$y_{a,b,c} = \frac{a}{g(a,b,c)} + \frac{\beta a}{g(a,b,c)} y_{a+1,b,c} + \frac{\gamma a}{g(a,b,c)} y_{a-1,b+1,c} + \frac{\mu b}{g(a,b,c)} y_{a,b-1,c+1} \tag{3.5}$$

for $(a,b,c) \in \Omega$ with $g(a,b,c) = (\beta+\gamma)a + \mu b > 0$. The boundary conditions are $y_{0,b,c} = 0$ and $y_{a,b,v} = 0$. In the case of the epidemic model, a solution could be obtained since the state space was finite and no state could be returned to once left. Although the latter property still holds, the branching process model has an infinite state space and so directly solving recurrence relation (3.5) is no longer possible. An approximate solution can be obtained by assuming that for $a + b > M$,

$$y_{a,b,c} \approx y_{M-b,b,c}.$$

Thus, the state space is truncated and a finite number of applications of recurrence relation (3.5) yield a solution. As M increases this approximation becomes more accurate, although the computation time increases proportionally to the number of states.

3.7.2 Effects of parameter changes

Using the recurrence relation method it is possible to explore the properties of χ numerically.

Figure 3.12 demonstrates the effect of increasing the response rate μ upon the expected effective severity generated by a branching process with one initial ancestor. When μ is zero, the intervention cannot occur and so the graph of χ

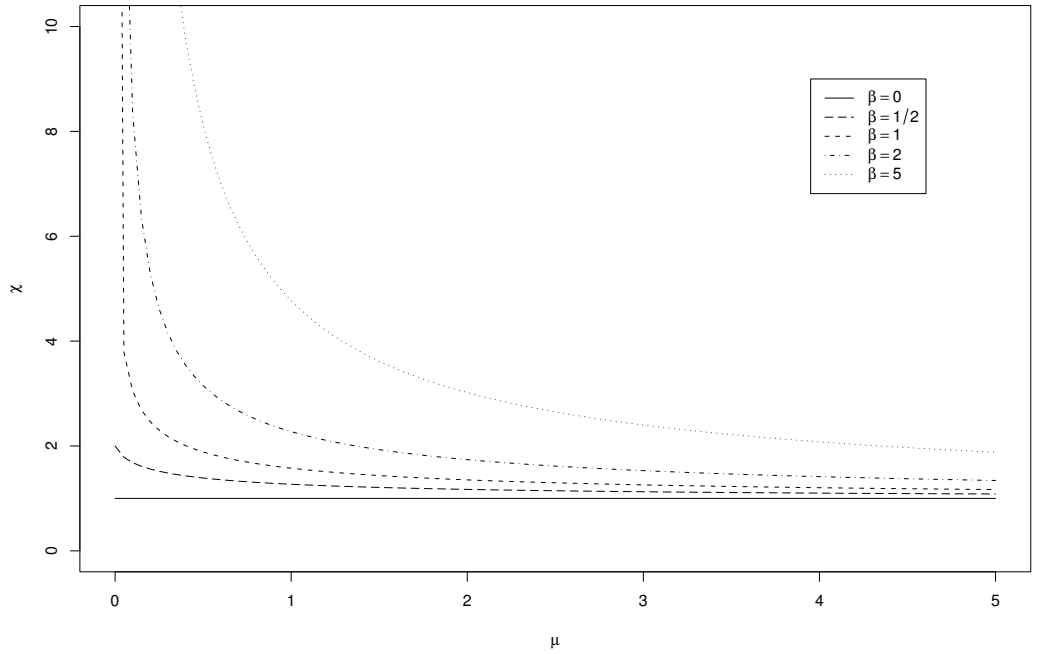

Figure 3.12: The expected effective severity χ against μ with $\gamma = 1$ and $i = v = 1$ calculated using $M = 1000$.

begins at its value for a branching process without intervention, which is infinite if $\beta \geq 1$. Note that when no intervention is considered and $\beta = 1$, although the expected severity is infinite, the severity is infinite with probability zero. As the response rate increases, the intervention occurs earlier and so χ decreases. As μ tends to infinity, χ tends to the expected severity until the vth removal (which is one here). As the infection rate β is increased, χ increases. When $\beta \geq 1$, the response rate μ becomes vital in determining the size of χ, since reducing the response rate by a small amount can cause a massive increase in χ. This highlights the importance of an early intervention to prevent the epidemic becoming rampant.

Figure 3.13 shows the effect of increasing the intervention trigger v on the ex-

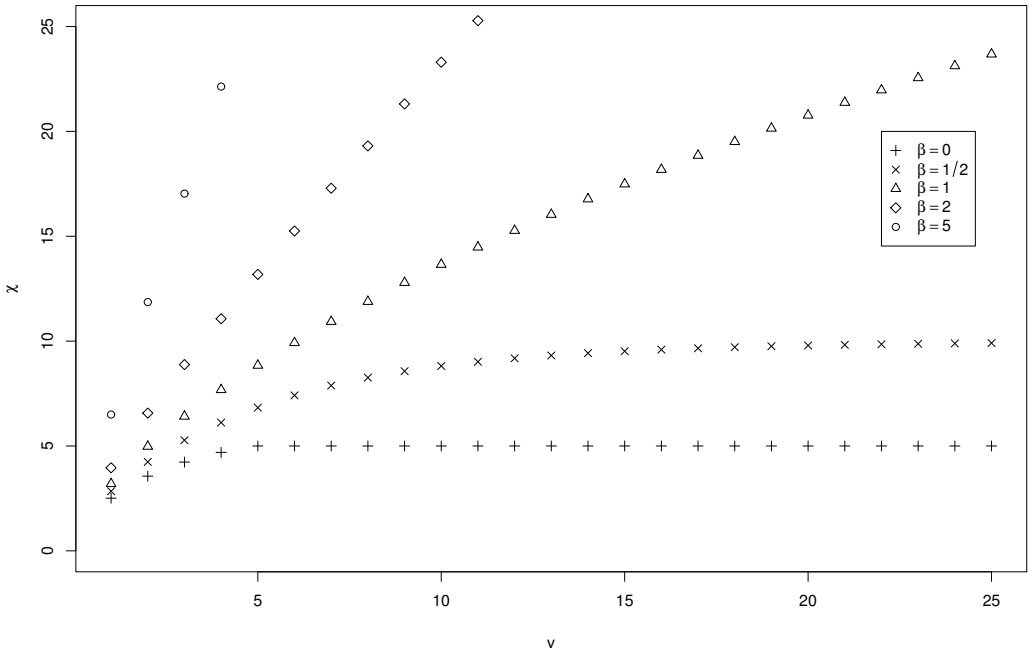

Figure 3.13: The expected effective severity χ against v with $\gamma = \mu = 1$ and $i = 5$ calculated using $M = 500$.

pected effective severity, χ, generated by the branching process. The graphs begin at the points given by $\mu = 1$ in figure 3.12 and then increase as v is increased. The graphs level off when the probability of having more than v individuals in the branching process becomes small, and the limit of the graphs is the expected severity generated by the branching process without intervention. When $\beta = 0$, χ reaches its limit once v has risen above 5, since only the 5 initial ancestors can be created. When $\beta \geq 1$ the expected total progeny of the branching process without intervention is infinite, and so χ continues to increase indefinitely as v increases. From a modelling point of view, figure 3.13 demonstrates that if the intervention is triggered when two cases have been observed instead of when one case has been observed, χ is significantly increased.

3.7.3 Deterministic approximations

In section 3.7.1 a recurrence relation was derived which could be solved for χ only by truncating the state space of the branching process. This section attempts to find bounds and approximations for χ by deriving and solving a set of differential equations for the mean trajectories of the numbers of each type of individual. For $\Delta t > 0$,

$$\begin{aligned}
\mathrm{E}[I(t+\Delta t)] &= \mathrm{E}[\mathrm{E}[I(t+\Delta t)|I(t)]] \\
&= \mathrm{E}[(I(t)+1)\Delta t\beta I(t) + (I(t)-1)\Delta t\gamma I(t) \\
&\quad +I(t)(1-\Delta t I(t)(\beta+\gamma))] + o(\Delta t) \\
&= \mathrm{E}[I(t)](\Delta t\beta - \Delta t\gamma + 1) + o(\Delta t)
\end{aligned}$$

After rearranging, and letting $\Delta t \to 0$, we obtain

$$\frac{\mathrm{dE}[I(t)]}{\mathrm{d}t} = (\beta-\gamma)\mathrm{E}[I(t)]$$

which implies that

$$\mathrm{E}[I(t)] = ie^{(\beta-\gamma)t},$$

since $I(0) = i$. A similar approach yields,

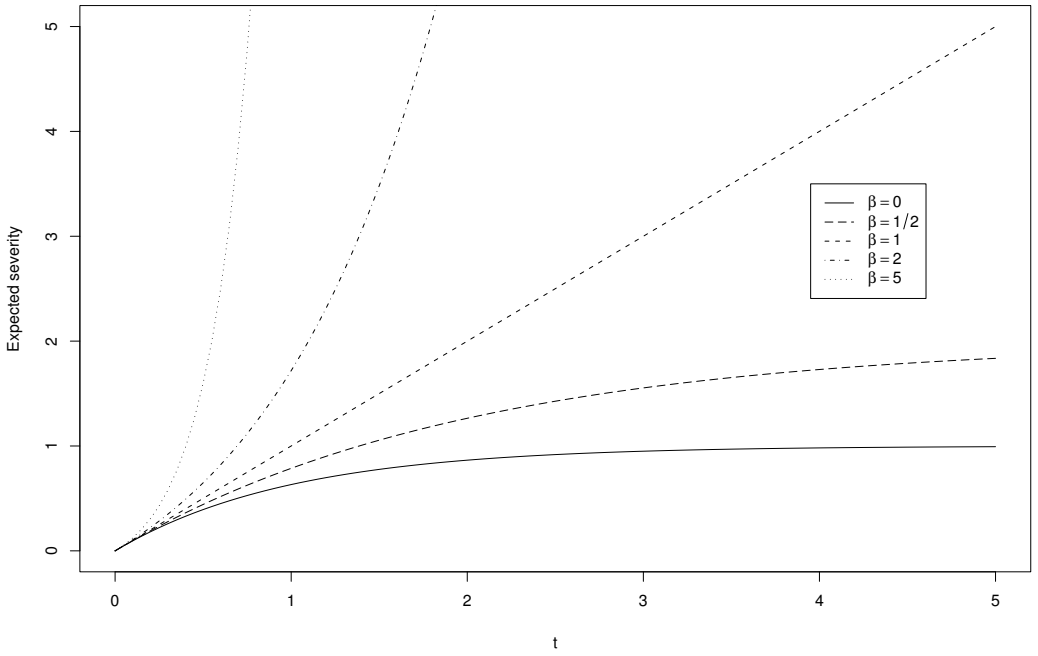

Figure 3.14: The expected severity generated by a branching process up to time t with $i = 1$ and $\gamma = 1$.

$$\mathrm{E}[R(t)] = \begin{cases} \gamma i t e^{-\mu t} & \beta = \gamma - \mu, \\ \frac{\gamma i (e^{(\beta-\gamma)t} - e^{-\mu t})}{\beta - \gamma + \mu} & \beta \neq \gamma - \mu. \end{cases}$$

$$\mathrm{E}[V(t)] = \begin{cases} \frac{\mu\gamma i}{\beta-\gamma+\mu}\left(t + \frac{e^{-\mu t}}{\mu}\right) & \beta = \gamma, \\ \frac{\mu\gamma i}{\beta-\gamma} t e^{-\mu t} & \beta = \gamma - \mu, \\ \frac{\mu\gamma i}{\beta-\gamma+\mu}\left(\frac{e^{(\beta-\gamma)t}}{\beta-\gamma} + \frac{e^{-\mu t}}{\mu}\right) & \text{otherwise.} \end{cases}$$

$$\mathrm{E}[A(t)] = \begin{cases} it & \beta = \gamma, \\ \frac{i(e^{(\beta-\gamma)t} - 1)}{\beta - \gamma} & \beta \neq \gamma. \end{cases}$$

Recall that $A(t) = \int_0^t I(u)\,\mathrm{d}u$.

Figure 3.14 shows the expected severity until time t generated by a branching process with one initial ancestor. Notice that when β is less than γ the expected

severity until time t forms a concave function, however, once the threshold $\beta = \gamma$ has been exceeded the function becomes convex. This follows from whether the expected number of infectives is increasing or decreasing in nature, which is clearly dictated by the relative sizes of β and γ.

Having derived the mean trajectories of the branching process, it is possible to try to use them to calculate approximations to the expected severity up to the intervention, $\chi = \mathrm{E}[A(T_v)]$. An approximation is required because the expected effective severity does not seem to be analytically tractable. First we compare some possible times at which the expected trajectory of the severity can be evaluated, to provide an estimate of χ, for different values of β. Since the intervention does not always occur, the stopping time T_v can be infinite with non-zero probability and so its expectation is infinite. Therefore define the time of the end of the epidemic to be

$$W_v = \inf\{t \geq 0 : V(t) = v \text{ or } I(t) = 0\},$$

which is almost surely finite. Another way around this problem is to consider only the realisations in which a useful intervention occurs, i.e. when there are still infectives at the time of intervention. This leads us to consider the random variable T_v given $I(T_v) > 0$. Finally, define t_1 to be the unique non-negative solution to the equation $v = \mathrm{E}[V(t_1)]$.

Table 3.1 shows possible times at which to evaluate the mean trajectory of the severity. Notice that for $\beta = 0$, $\mathrm{E}[T_v | I(T_v) > 0]$ is not defined since for $i = v = 1$ it is impossible for the event $I(T_v) > 0$ to occur. The table suggests

	$\beta = 0$	$\beta = 1/2$	$\beta = 1$	$\beta = 2$	$\beta = 5$
$\mathrm{E}[W_v]$	1.0005	0.9229	0.8557	0.7500	0.5559
$\mathrm{E}[T_v \mid I(T_v) > 0]$	-	1.4623	1.2387	0.9766	0.6396
t_1	∞	1.9340	1.4738	1.0792	0.6681

Table 3.1: Comparison of possible times at which to evaluate the mean trajectory of the severity, with $\gamma = 1$, $\mu = 2$ and $i = v = 1$. The expectations were simulated using one million realisations of the branching process.

that

$$\mathrm{E}[W_v] \leq \mathrm{E}[T_v \mid I(T_v) > 0] \leq t_1.$$

The first of these inequalities makes sense, as $W_v = T_v$ when $I(T_v) > 0$ and W_v is likely to be smaller if the branching process dies out before the intervention occurs. The second inequality also makes sense as the function $\mathrm{E}[V(t)]$ includes the case in which the branching process dies out and so $\mathrm{E}[V(t)]$ reaches v slower than it might otherwise.

To simplify the notation in the following, define

$$f(t) = \mathrm{E}[A(t)] = \frac{i(e^{(\beta-\gamma)t} - 1)}{\beta - \gamma}.$$

Table 3.2 gives the function f evaluated at the times given in table 3.1 together with simulations and approximations for $\chi = \mathrm{E}[A(T_v)]$.

Table 3.2 suggests that the true value for χ lies between $f(\mathrm{E}[T_v \mid I(T_v) > 0])$ and $f(t_1)$. Since $\mathrm{E}[T_v \mid I(T_v) > 0]$ has been found using simulations, it does not provide a useful lower bound for χ, as it is simpler to simulate χ. The upper bound $f(t_1)$ however, appears to be very close to χ and is the solution to an

	$\beta = 0$	$\beta = 1/2$	$\beta = 1$	$\beta = 2$	$\beta = 5$
$f(\mathrm{E}[W_v])$	0.6323	0.7393	0.8557	1.1171	2.0598
$f(\mathrm{E}[T_v \mid I(T_v) > 0])$	-	1.0373	1.2387	1.6553	2.9791
$f(t_1)$	1.0000	1.2395	1.4737	1.9422	3.3686
χ (simulated)	1.0005	1.1733	1.3539	1.7372	3.0143
χ (approximated)	1.0000	1.1719	1.3534	1.7394	3.0181

Table 3.2: Comparison of estimates for χ against simulated values and approximated values. The simulated values were calculated using one million realisations of the branching process and the approximated values were calculated using the state space truncation method described in section 3.7.1 with M=250. The parameters used are $\gamma = 1$, $\mu = 2$ and $i = v = 1$.

equation and is easy to calculate and therefore useful in practice. By varying the parameters i and v it is possible to produce variations of table 3.2 that conform to a trend. If the branching process is much more likely to die out before the intervention is applied then $f(t_1)$ provides a sharp upper bound for χ. This is because the expected trajectory of the severity (the function f) will rapidly approach the total severity of a branching process without intervention and t_1 will be large or infinite. This implies that $f(t_1)$ and χ will both be close to the expected severity generated by the subcritical branching process.

The other situation in which $f(t_1)$ will have a value close to χ is when extinction of the branching process is very unlikely. In this case the number of individuals in the branching process will quickly become large and so $V(t)$ is likely to follow a path similar to $\mathrm{E}[V(t)]$ and $A(t)$ is likely to follow a path similar to $\mathrm{E}[A(t)]$. The former of these suggests that T_v will be close to t_1 in most of the realisations of the branching process and the latter suggests that $f(t_1)$ will accurately reflect the severity produced in the same realisations.

The only remaining situation, in which $f(t_1)$ is not a very good estimate for χ, is when the probability of extinction of the branching process is approximately equal to the probability of intervention. In this case $V(t)$ rises slowly to v (instead of quickly or not at all) and t_1 is unrealistically large. This causes $f(t_1)$ to overestimate χ since f is strictly increasing.

In conclusion $f(t_1)$ appears to be a useful upper bound on the expected effective severity for the branching process model with exponential removed periods, particularly if the branching process is very likely to die out, or to grow rapidly. However, the recurrence relation method derived in section 3.7.1 provides a more accurate approximation for χ.

3.8 Branching process approximation to the epidemic with exponential infectious periods and constant removed periods.

We now change the distribution of the time that individuals spend in the removed category from an exponential distribution to a constant for the branching process described in section 3.7. Let $T_R = L$ and define T_v and U_v to be the stopping times

$$\begin{aligned} T_v &= \inf\{t \geq L : V(t) = v\}, \\ U_v &= \inf\{t \geq 0 : R(t) + V(t) = v\}, \end{aligned}$$

so that U_v represents the time of the vth death in the branching process and T_v represents the time that the vth individual enters the response category. Using these stopping times it becomes possible to follow the plan of attack used in section 3.5 and to express the expected effective severity χ in terms of $\mathrm{E}[A(U_v)]$, $\mathrm{E}\left[\int_{U_v}^{T_v} I(u)\,\mathrm{d}u \middle| I(U_v) = k\right]$ and the distribution of $I(U_v)$. These three quantities are derived in the next three subsections.

$$\begin{aligned} \chi &= \mathrm{E}[A(T_v)] \\ &= \mathrm{E}[A(U_v)] + \mathrm{E}\left[\int_{U_v}^{T_v} I(u)\,\mathrm{d}u\right] \\ &= \mathrm{E}[A(U_v)] + \sum_{k=0}^{\infty} \mathrm{E}\left[\int_{U_v}^{T_v} I(u)\,\mathrm{d}u \middle| I(U_v) = k\right] \mathrm{P}(I(U_v) = k) \end{aligned}$$

Notice that it is not immediately clear what happens when v deaths do not occur, so that $U_v = \infty$. Since $\lim_{t\to\infty} I(t) = 0$ almost surely, it makes sense to

define $I(U_v) = 0$ in this case. This implies that the expected severity generated between U_v and T_v is also zero, which makes sense. Therefore given that v deaths do not occur, χ reduces to $\mathrm{E}[A(U_v)]$.

3.8.1 The expected severity up to the vth removal.

Using the random time transform of Watson (1980) for the present branching process model, we again find that the severity between deaths has an exponential distribution with mean γ^{-1}, up to the death of the last individual (see section 3.5.1). Assuming that the number of individuals stays above zero, the probability that a birth occurs before a death from any state of the branching process is $\beta/(\beta+\gamma)$. Thus, the probability that the total progeny of branching process is k (the probability that k individuals are born including the i initial ancestors), is equal to

$$\left(\frac{\gamma}{\beta+\gamma}\right)^{k}\left(\frac{\beta}{\beta+\gamma}\right)^{k-i} N_{i,k}$$

for $i > 0$ and $k \geq i$. The multiplier $N_{i,k}$ is an integer representing the number of possible paths through the state space that the number of infectives can take from its initial value of i to its final value of 0 with exactly k deaths. Once the number of infectives has reached 0 there can be no more deaths and so the path cannot reach zero until its final step. Also, if there are $k \geq i$ deaths then there must be $k-i$ births and so the path must contain $2k-i$ steps in total, the last one of which is a death. Thus,

$$N_{i,k} \;=\; |\{\text{paths on } \mathbb{N} \text{ from } i \text{ to } 1 \text{ in } 2k-i-1 \text{ steps}\}|$$

$$
\begin{aligned}
&= |\{\text{paths on } \mathbb{Z} \text{ from } i \text{ to } 1 \text{ in } 2k-i-1 \text{ steps}\}| \\
&\quad -|\{\text{paths on } \mathbb{Z} \text{ reaching } 0 \text{ from } i \text{ to } 1 \text{ in } 2k-i-1 \text{ steps}\}| \\
&= |\{\text{paths on } \mathbb{Z} \text{ from } i \text{ to } 1 \text{ in } 2k-i-1 \text{ steps}\}| \\
&\quad -|\{\text{paths on } \mathbb{Z} \text{ from } i \text{ to } -1 \text{ in } 2k-i-1 \text{ steps}\}|
\end{aligned}
$$

by the reflection principle. A path on $\mathbb{Z}$ from a to $b \leq a$ in $a-b+2c$ steps contains c births and $a-b+c$ deaths, in any order. Thus, the number of such paths is $\binom{a-b+2c}{c} = \binom{a-b+2c}{a-b+c}$. Therefore,

$$
\begin{aligned}
N_{i,k} &= \binom{2k-i-1}{k-1} - \binom{2k-i-1}{k} \\
&= \frac{i}{k}\binom{2k-i-1}{k-1}.
\end{aligned}
$$

The conventions used here are that there is exactly one path of zero length between 1 and 1 (e.g. $k = i = 1$); and when i exceeds $2k-1$ there are no paths. Rajarshi (1981) proves this result for $N_{i,k}$ by relating it to the 'ballot theorem' in Feller (1971): if the winner in a ballot totalling $2x+y$ votes wins by y votes, the number of ways that the winner will be ahead throughout the counting is equal to $\frac{y}{2x+y}\binom{2x+y}{x}$. The mass function of the total progeny of the branching process can also be found using Theorem 2.11.2 of Jagers (1975).

We can now use the preceding results to find the expected severity until the vth removal, by conditioning on the total progeny of the branching process.

$$
\begin{aligned}
&\mathrm{E}[A(U_v)] \\
&= \mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right]
\end{aligned}
$$

$$
\begin{aligned}
&= \sum_{k=i}^{v-1} \frac{k}{\gamma} \mathrm{P}(\text{Total Progeny } = k) + \frac{v}{\gamma}(1 - \mathrm{P}(\text{Total Progeny } < v)) \\
&= \frac{v}{\gamma} + \sum_{k=i}^{v-1} \frac{k-v}{\gamma} \left(\frac{\gamma}{\beta+\gamma}\right)^{k} \left(\frac{\beta}{\beta+\gamma}\right)^{k-i} \left(\binom{2k-i-1}{k-1} - \binom{2k-i-1}{k}\right).
\end{aligned}
$$

Obviously, if $i \geq v$ then this simplifies to v/γ.

3.8.2 The expected severity until time L.

We now derive the expected severity between U_v and T_v, conditional on the number of individuals alive at time U_v. Since the time spent in the removed category is always equal to the constant L, the time at which the vth individual enters the response category (T_v) occurs exactly L time units after the vth death (time U_v), i.e. $T_v = U_v + L$. Thus, it is sufficient to find the expected severity of a branching process without intervention between 0 and L (by the time homogeneity property) given the number of individuals alive at time 0.

For $i \geq 1$ and $t \geq 0$ define

$$
x_i(t) = \mathrm{E}\left[\int_0^t I(u)\,\mathrm{d}u \middle| I(0) = i\right],
$$

then the backward equation can be formed as follows.

$$
\begin{aligned}
&x_i(t+\Delta t) \\
&= \mathrm{E}\left[\int_0^{t+\Delta t} I(u)\,\mathrm{d}u \middle| I(0) = i,\ \text{birth in } (0,\Delta t]\right] \mathrm{P}(\text{birth in } (0,\Delta t]) \\
&\quad + \mathrm{E}\left[\int_0^{t+\Delta t} I(u)\,\mathrm{d}u \middle| I(0) = i,\ \text{death in } (0,\Delta t]\right] \mathrm{P}(\text{death in } (0,\Delta t]) \\
&\quad + \mathrm{E}\left[\int_0^{t+\Delta t} I(u)\,\mathrm{d}u \middle| I(0) = i,\ \text{no event in } (0,\Delta t]\right] \mathrm{P}(\text{no event in } (0,\Delta t])
\end{aligned}
$$

$$
\begin{aligned}
&+\mathrm{E}\left[\int_0^{t+\Delta t} I(u)\,\mathrm{d}u \Big| I(0)=i, >1 \text{ events in } (0,\Delta t]\right] \mathrm{P}(>1 \text{ events in } (0,\Delta t]) \\
= \;& \Delta t\beta i(\Delta t(i+1/2)+x_{i+1}(t)) + \Delta t\gamma i(\Delta t(i-1/2)+x_{i-1}(t)) \\
&+(1-\Delta t(\beta+\gamma)i)(\Delta t i + x_i(t)) + o(\Delta t) \\
= \;& \Delta t\beta i x_{i+1}(t) + \Delta t\gamma i x_{i-1}(t) + (1-\Delta t(\beta+\gamma)i)(\Delta t i + x_i(t)) + o(\Delta t).
\end{aligned}
$$

This implies that

$$
\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = \beta i x_{i+1}(t) + \gamma i x_{i-1}(t) + i - (\beta+\gamma) i x_i(t)
$$

Since this is the branching process model,

$$
x_i(t) = i x_1(t) \tag{3.6}
$$

so that,

$$
\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} = (\beta-\gamma)x_1(t) + 1. \tag{3.7}
$$

Equation (3.7) has solution

$$
x_1(t) = \begin{cases} t & \beta = \gamma, \\ \frac{1}{\beta-\gamma}\left(e^{(\beta-\gamma)t}-1\right) & \beta \neq \gamma, \end{cases}
$$

and thus from (3.6) we obtain

$$
x_i(L) = \begin{cases} iL & \beta = \gamma, \\ \frac{i}{\beta-\gamma}\left(e^{(\beta-\gamma)L}-1\right) & \beta \neq \gamma. \end{cases} \tag{3.8}
$$

In order to find the expected severity between U_v and T_v, equation (3.8) must be multiplied by $\mathrm{P}(I(U_v)=i)$ and summed over $i=0,1,2,\ldots$. Since $x_i(L)$ is linear in i, it is sufficient to work out the expected number of individuals alive

just after the vth death, i.e.

$$\begin{aligned} \mathrm{E}\left[\int_{U_v}^{T_v} I(u)\,\mathrm{d}u\right] &= \sum_{i=0}^{\infty} x_i(L)\mathrm{P}(I(U_v)=i) \\ &= \sum_{i=0}^{\infty} i x_1(L)\mathrm{P}(I(U_v)=i) \\ &= x_1(L)\mathrm{E}[I(U_v)]. \end{aligned}$$

This expectation is properly defined since $U_v = \infty$ implies that $I(U_v) = 0$ almost surely. We now turn to the evaluation of $\mathrm{E}[I(U_v)]$.

3.8.3 The expected number of individuals alive after the vth death.

The expected number of individuals alive just after the vth death can be found by conditioning on the path that the embedded discrete time branching process takes. This process is a random walk on $\mathbb{N} \cup \{0\}$ with the probability of an upward jump as $\beta/(\beta+\gamma)$; the probability of a downward jump as $\gamma/(\beta+\gamma)$ and an absorbing barrier at zero. Recall from section 3.8 that we need not consider paths in which v removals do not occur since $I(U_v) = 0$ in this case.

$$\mathrm{E}[I(U_v)] = \sum_{d \in D} I(U_v; d)\mathrm{P}(\text{the process takes path } d),$$

where $I(U_v; d)$ is the number of individuals alive after the vth death in the path d; and D is the set of valid paths in which v deaths occur and in which $I(U_v; d) > 0$.

Next, group together paths with the same values of $I(U_v; d)$ by noticing that

the number of births before U_v determines $I(U_v; d)$ and the probabilities of observing these paths are equal. A path containing l births before the vth death contains $l + v$ steps (ending with a death); starts with i individuals and ends with $i + l - v$ individuals, where $i + l - v = I(U_v) > 0$. Thus,

$$\mathrm{E}[I(U_v)] = \sum_{l=v-i+1}^{\infty} (i + l - v) \left(\frac{\beta}{\beta+\gamma}\right)^l \left(\frac{\gamma}{\beta+\gamma}\right)^v N_{i,l,v}$$

where $N_{i,l,v}$ represents the number of permitted paths.

$$\begin{aligned} N_{i,l,v} &= |\{\text{paths on } \mathbb{N} \text{ from } i \text{ with } l \text{ births and } v \text{ deaths ending with a death}\}| \\ &= |\{\text{paths on } \mathbb{N} \text{ from } i \text{ with } l \text{ births and } v-1 \text{ deaths}\}| \\ &= |\{\text{paths on } \mathbb{Z} \text{ from } i \text{ with } l \text{ births and } v-1 \text{ deaths}\}| \\ &\quad -|\{\text{paths on } \mathbb{Z} \text{ from } i \text{ with } l \text{ births and } v-1 \text{ deaths reaching } 0\}| \\ &= \binom{l+v-1}{v-1} - \binom{l+v-1}{v-i-1}. \end{aligned}$$

The second combinatorial term is found by applying the reflection principle. So,

$$\mathrm{E}[I(U_v)] = \sum_{l=v-i+1}^{\infty} (i+l-v) \left(\frac{\beta}{\beta+\gamma}\right)^l \left(\frac{\gamma}{\beta+\gamma}\right)^v \left[\binom{l+v-1}{v-1} - \binom{l+v-1}{v-i-1}\right]. \tag{3.9}$$

This infinite sum can be expressed as a finite sum with the application of two identities.

Consider a random walk on $\mathbb{Z}$ that starts at a and has the probability of an upward jump as $\beta/(\beta+\gamma)$. The expected location of this random walk after

$r > 0$ downward jumps is

$$\sum_{l=0}^{\infty}(a+l-r)\left(\frac{\beta}{\beta+\gamma}\right)^{l}\left(\frac{\gamma}{\beta+\gamma}\right)^{r}\binom{l+r-1}{r-1},$$

and also

$$\mathrm{E}[a+(X_1-1)+(X_2-1)+\ldots+(X_r-1)] = a+r\mathrm{E}[X_1]-r$$

where X_j is the number of upward jumps (births) between the $(j-1)$th jump down (death) and the jth jump down. Thus, X_1 has a geometric distribution with $\mathrm{P}(X_1=k)=\frac{\gamma\beta^k}{(\beta+\gamma)^{k+1}}$, and so $\mathrm{E}[X_1]=\frac{\beta}{\gamma}$. This implies that

$$a+\frac{r(\beta-\gamma)}{\gamma} = \sum_{l=0}^{\infty}(a+l-r)\left(\frac{\beta}{\beta+\gamma}\right)^{l}\left(\frac{\gamma}{\beta+\gamma}\right)^{r}\binom{l+r-1}{r-1}. \qquad (3.10)$$

Next, let $l \mapsto k+i$:

$$a+\frac{r(\beta-\gamma)}{\gamma} = \sum_{k=-i}^{\infty}(a+i+k-r)\left(\frac{\beta}{\beta+\gamma}\right)^{k+i}\left(\frac{\gamma}{\beta+\gamma}\right)^{r}\binom{k+i+r-1}{r-1},$$

and then set $a=-i$ and $r=v-i$ (for $v>i$) to give,

$$\left(\frac{(v-i)(\beta-\gamma)}{\gamma}-i\right)\left(\frac{\gamma}{\beta}\right)^{i} = \sum_{k=-i}^{\infty}(i+k-v)\left(\frac{\beta}{\beta+\gamma}\right)^{k}\left(\frac{\gamma}{\beta+\gamma}\right)^{v}\binom{k+v-1}{v-i-1}. \qquad (3.11)$$

Applying equation (3.10) to the first combinatorial term in (3.9) and equation (3.11) to the second combinatorial term in (3.9) (which is zero unless $v>i$)

yields

$$\mathrm{E}[I(U_v)] = \begin{cases} i + \frac{v(\beta-\gamma)}{\gamma} & v \leq i, \\ i + \frac{v(\beta-\gamma)}{\gamma} - \left(\frac{(v-i)(\beta-\gamma)}{\gamma} - i\right)\left(\frac{\gamma}{\beta}\right)^i & \\ \quad - \sum_{l=0}^{v-i-1} (i+l-v)\left(\frac{\beta}{\beta+\gamma}\right)^l \left(\frac{\gamma}{\beta+\gamma}\right)^v \binom{l+v-1}{v-1} & \\ \quad + \sum_{l=-i}^{v-i-1} (i+l-v)\left(\frac{\beta}{\beta+\gamma}\right)^l \left(\frac{\gamma}{\beta+\gamma}\right)^v \binom{l+v-1}{v-i-1} & v > i. \end{cases}$$

Taking this result with the two previous parts gives an explicit expression for the expected severity until intervention.

$$\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u\right] = \mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] + E[I(U_v)]x_1(L)$$

This lengthy formula simplifies greatly for the special case in which $v \leq i$ (including the practically useful case $i = v = 1$) to

$$\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u\right] = \begin{cases} \frac{v}{\gamma} + iL & \beta = \gamma, \\ \frac{v}{\gamma} + \left(i + \frac{v(\beta-\gamma)}{\gamma}\right)\left(\frac{e^{(\beta-\gamma)L}-1}{\beta-\gamma}\right) & \beta \neq \gamma. \end{cases}$$

3.8.4 Effects of parameter changes

Figure 3.15 shows the effect of increasing the constant time L that an individual spends in the removed category. There is a remarkable distinction between the subcritical and supercritical branching processes, with the limiting case ($\beta = \gamma$) having gradient one. The graph therefore highlights the importance of an early intervention in the supercritical branching process case, as the expected effective severity rises extremely steeply as L is increased. This also illustrates the importance of minimising the number of contacts between individuals to

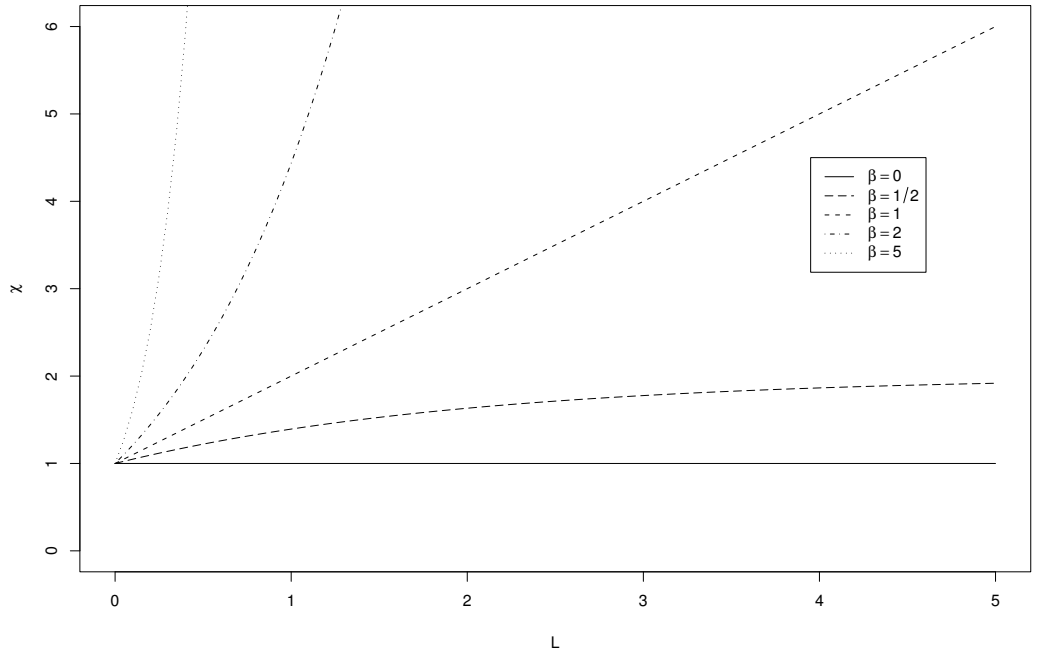

Figure 3.15: The expected effective severity χ against L with $i = 1$, $v = 1$ and $\gamma = 1$.

reduce the value of β as much as possible.

Figure 3.16 demonstrates the effect of increasing the intervention trigger v on the expected effective severity. In this graph, five initial infectives were assumed, so that in the lower part of the graph (1-5) intervention is certain and in the upper part (6+) the branching process may become extinct before the intervention trigger has been reached. This appears to make no significant difference for $\beta > 0$, although close examination reveals a very minor reduction in the gradient after $v = 5$. As v tends to infinity, the graphs produced by subcritical branching processes tend to finite limits, given by the expected severity generated by these processes without intervention. For the other branching processes ($\beta \geq \gamma$), the graphs tend to infinity as v tends to infinity, again reflecting

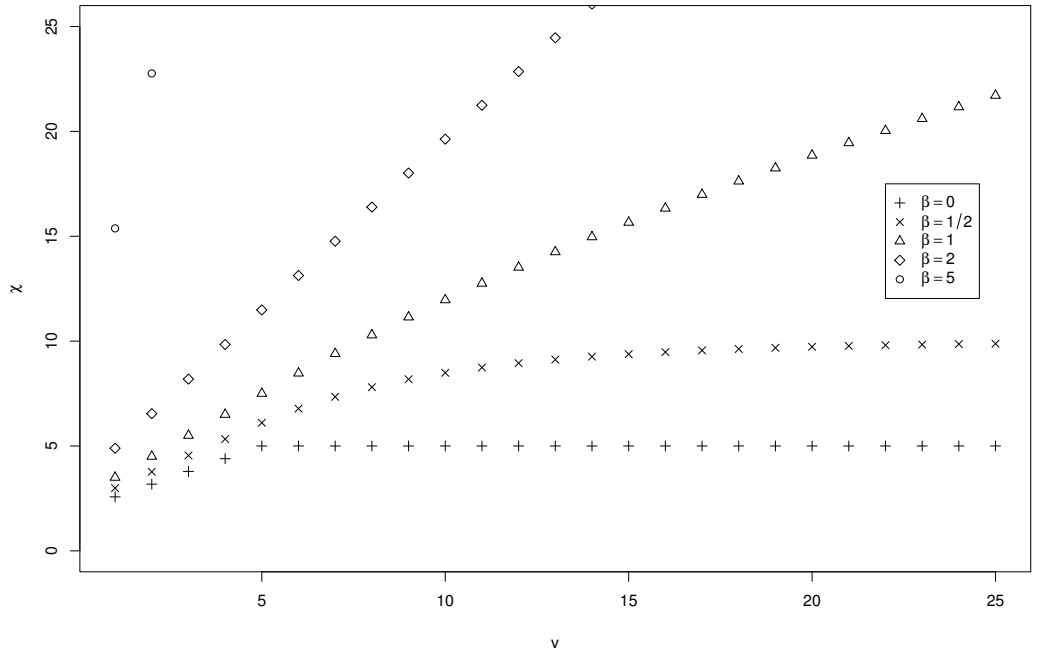

Figure 3.16: The expected effective severity χ against v with $i = 5$, $\gamma = 1$ and $L = 1/2$.

the the expected severity without intervention.

3.9 Comparison of the exponential and constant removed periods

Methods have been produced for finding the expected effective severity when the removed periods have an exponential distribution and when they are of constant length. This section compares the effect that the removed period distribution has on the expected effective severity.

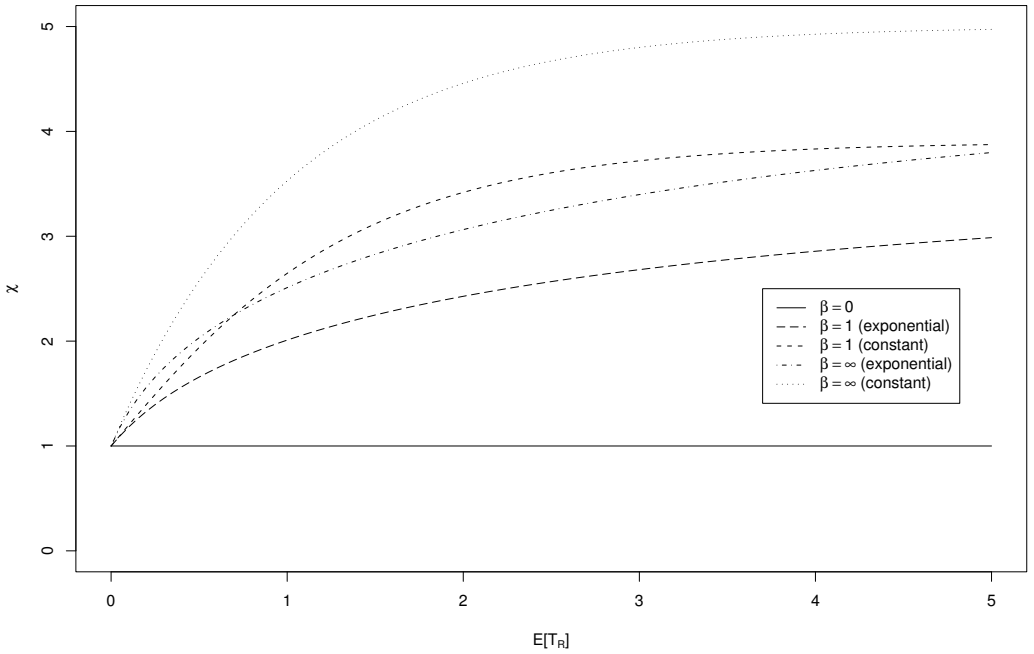

Figure 3.17: The expected effective severity χ against $\mathrm{E}[T_R]$ for epidemics with exponential and constant removed periods with $n = 4$, $i = v = 1$ and $\gamma = 1$.

3.9.1 Epidemic model

Figure 3.17 compares the expected effective severity, χ, generated by the epidemic with exponential and constant removed periods when the contact rate β is zero, one and infinity. When β is zero, the initially infectious individual is removed before infecting any other individuals, and so this individual is the only one to contribute to the severity. Since this individual is removed before the intervention occurs, the severity is independent of the removed period distribution. When β is greater than zero, the removed period distribution does affect χ. The graph suggests that χ is larger when the removed period has a constant length than when it is distributed exponentially. A likely explanation is as follows. In the former case, the intervention is certain to be set off by the

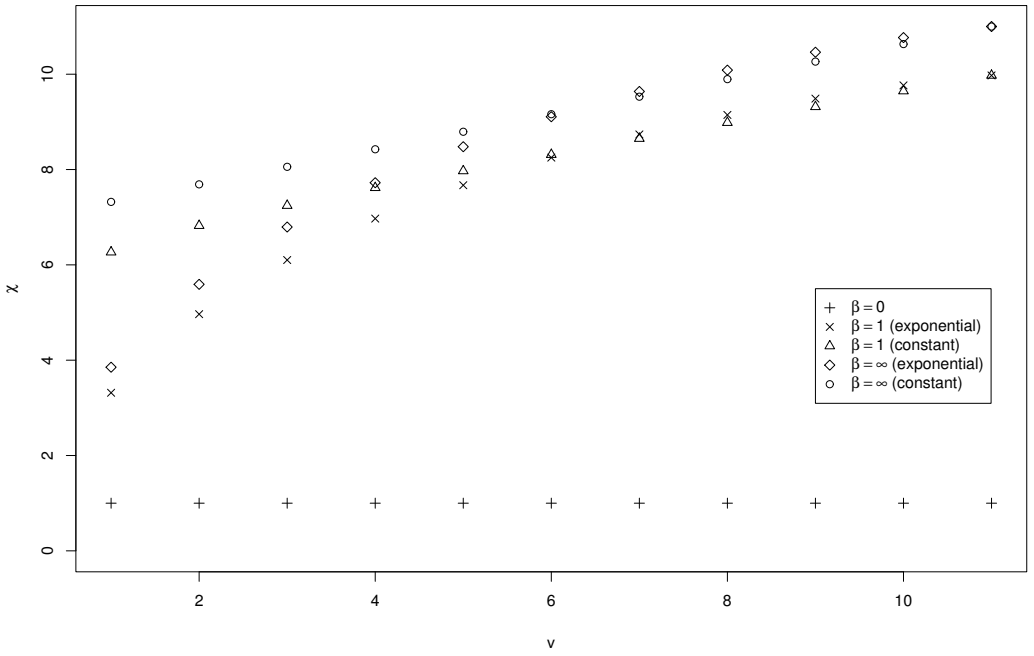

Figure 3.18: The expected effective severity χ against v for epidemics with exponential and constant removed periods with $n = 10$, $i = 1$ and $\gamma = \mathrm{E}[T_R] = 1$.

first individual to be removed. When the removed period has an exponential distribution, there is a positive probability of an individual that was removed later 'overtaking' the first individual to be removed and setting off the intervention earlier. Figure 3.17 also suggests that as the expected removed period tends to infinity, the expected effective severities of the two removed period distributions tend to the same limit. This is because an infinite removed period prevents the intervention from occurring and so χ tends to the expected severity for an epidemic without intervention - which is independent of individuals that have been removed.

Figure 3.18 provides further insights. It demonstrates the effect of increasing the intervention threshold v on the expected severities created by constant and

exponential removed periods. Notice that for small v, the constant removed period creates the larger expected severity; however, as v approaches the whole household, the exponential removed period creates the larger expected severity. This trend can be explained as follows.

Since the propagation of the epidemic is independent of the removed periods except for the timing of the intervention, the random variable T_v determines the severity. Define the time at which individual j is removed to be W_j, for $j = 1, \ldots, n+i$ with $W_j = \infty$ if they are never removed. Then, T_v is the vth smallest instance of the random variables $W_j + T_R^{(j)}$, where $T_R^{(j)}$ is the removed period of individual j. When v is small, the variation in the exponential distribution means that T_v for exponential distribution is likely to be smaller than $W_v + \mathrm{E}[T_R]$, the equivalent for the constant removed period. However, the vth smallest instance of $W_j + T_R^{(j)}$ is also the $n + i - v$th largest instance, and so when v is large, the fact that some of the exponential distributions are likely to be higher than the constant removed period, delays the intervention in the same way.

3.9.2 Branching process approximation

Figure 3.19 demonstrates the effect of changing the removed period distribution on the graph of the expected effective severity χ as the expected removed period is altered. When $\beta > 0$ the curves for exponential and constant removed period distributions rapidly diverge, with the constant removed period distribution causing greater severity. For the supercritical branching process ($\beta > 1$) the constant removed period yields a convex function in $\mathrm{E}[T_R]$, however the corresponding function for the exponential removed period appears to be concave.

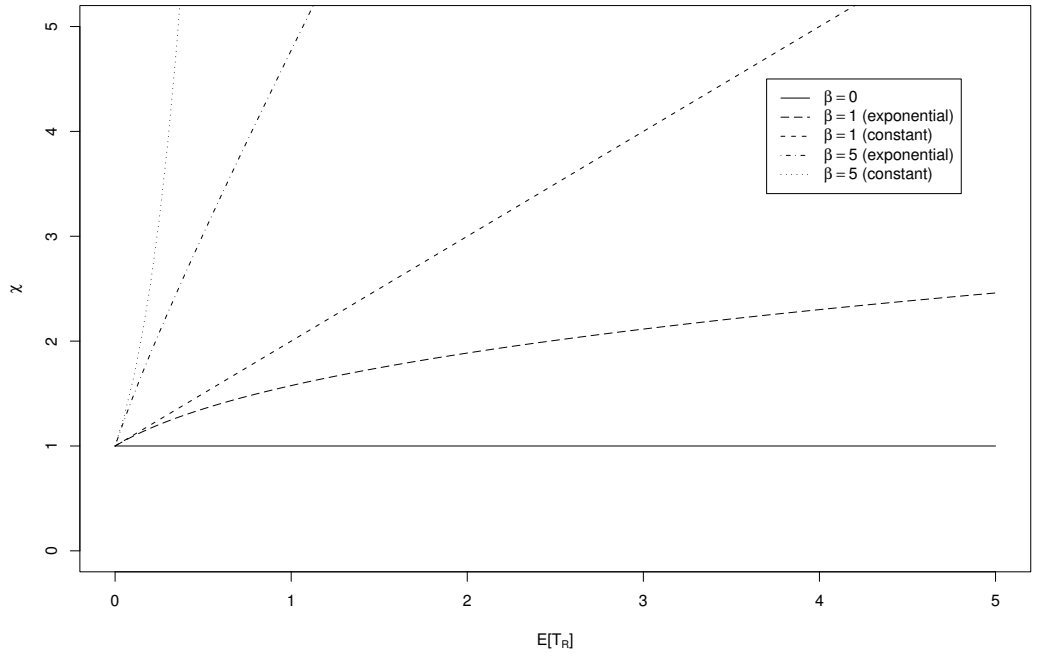

Figure 3.19: The expected effective severity χ against $\mathrm{E}[T_R]$ for branching processes with exponential and constant removed periods with $i = v = 1$ and $\gamma = \mathrm{E}[T_R] = 1$.

Figure 3.20 displays the effect of increasing the intervention trigger v on χ. For the critical and subcritical processes the intervention time is predominantly determined by the removal times due to the slow rate at which the epidemic propagates. In the supercritical case shown ($\beta = 5$) it is very likely that there will be individuals removed shortly after the vth removal. This increases the likelihood that the intervention will be triggered earlier for the exponential removed period than for the constant removed period, as these individuals may trigger the intervention in the exponential case.

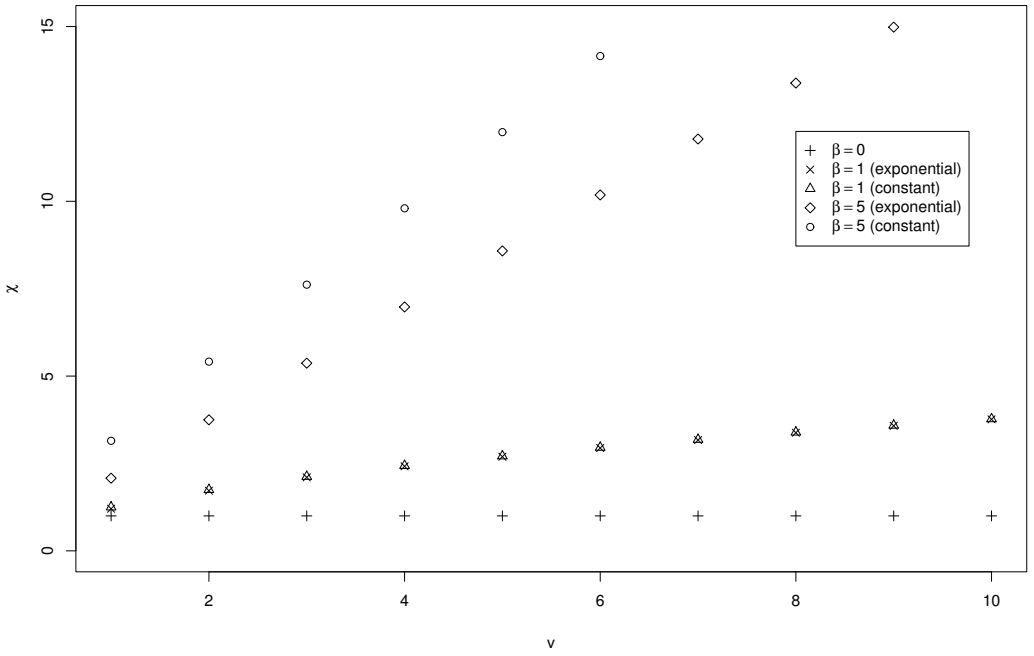

Figure 3.20: The expected effective severity χ against v for branching processes with exponential and constant removed periods with $i = 1$, $\gamma = 1$ and $\mathrm{E}[T_R] = 4$.

3.9.3 Conjectures

It is conjectured that the constant removed period distribution gives the largest possible expected effective severity for the branching process approximation to the epidemic model when the expected removed period is held fixed. The same belief is held for the epidemic model with the restriction $v = 1$. If true, these conjectures would enable the constant removed period to be used to calculate an upper bound on the expected severity when little is known of the removed period distribution.

3.10 Discrete time models

Thus far, this chapter has been concerned only with a continuous time model, however, discrete time epidemic models are also used. This section attempts to incorporate a delay between the detection of an infective and the subsequent intervention into discrete time models. In some respects discrete time models represent a more realistic analogy to practical situations than continuous time models. For instance, continuous time models usually assume a constant rate of mixing all of the time, ignoring the differences between daytime and nighttime behaviour that fit intuitively into a discrete time model.

This section develops a general approach for calculating the expected severity of discrete time epidemic models. Interventions are incorporated as absorbing states which produce no further severity, and as long as an absorbing state is ultimately accessible from any part of the state space, the expected severity can be concisely stated. The application of this formula is then illustrated with the example of a chain binomial epidemic model that incorporates a delay before the intervention can be applied. The effect of altering the expected length of this delay is then explored. Finally, the threshold parameter is calculated for a model based on the discrete time model used by Longini *et al.* (2004) to predict the effect of antiviral agents on pandemic influenza.

3.10.1 A general approach

In order to incorporate interventions (at a Markov stopping time) into a discrete time epidemic model, form a new Markov process with an absorbing state representing the intervention having occurred and define this state to contribute

nothing to the severity. When the epidemic process enters this absorbing state, the epidemic is effectively over. This might mean that some of the states are now inaccessible to the epidemic and therefore do not need to be considered as part of the state space, greatly simplifying calculations. For example, when the intervention is triggered after the first removal, states containing two or more removed individuals are inaccessible to the process, and so can be ignored.

Next, we derive a method of finding the expected severity for an epidemic process.

Let $\{X_t : t \geq 0\}$ be a discrete time Markov process with finite state space Ω and transition matrix P, initially distributed according to the row vector $\boldsymbol{\alpha}$. Associate with this Markov process a function $s : \Omega \to \mathbb{R}$ and form a row vector $\boldsymbol{s} = [s(x)]_{x \in \Omega \setminus A}$ where $A \subseteq \Omega$ is the set of absorbing states, and assume that $s(a) = 0$ for all $a \in A$. Next define Q to be the submatrix of P on $\Omega \setminus A$ and so Q is a substochastic matrix. To avoid the possibility that $\Omega \setminus A$ contains any absorbing states or any closed subsets of states, it is necessary to assume that the following condition holds.

For each $x \in \Omega \setminus A$ there exists a path with positive probability of occurring, from x to some state $a \in A$.

This condition can be restated in terms of the matrix Q as follows.

For each $x \in \Omega \setminus A$ there exists a $y \in \Omega \setminus A$ and a $k \in \mathbb{N} \cup \{0\}$ such that the probability of going from x to y in k steps is strictly positive and the state y satisfies $\sum_{j \in \Omega \setminus A} q_{y,j} < 1$.

Clearly this condition implies that Q is strictly substochastic, i.e. that at least one row of the matrix Q must sum to strictly less than one. In Appendix C, it

is shown that for a substochastic Q with the above property, the matrix $(I-Q)$ is non-singular and that

$$(I-Q)^{-1} = \sum_{t=0}^{\infty} Q^t.$$

This can be used to calculate the expected 'severity' (the expected cumulation of $s(X_t)$ until absorption) of this Markov process as follows.

$$\begin{aligned} \mathrm{E}\left[\sum_{t=0}^{\infty} s(X_t)\right] &= \sum_{t=0}^{\infty} \mathrm{E}\left[s(X_t)\right] \\ &= \sum_{t=0}^{\infty} \sum_{x\in\Omega} \mathrm{P}(X_t = x | X_0 \sim \boldsymbol{\alpha}) s(x) \\ &= \sum_{t=0}^{\infty} \sum_{x\in\Omega\setminus A} \mathrm{P}(X_t = x | X_0 \sim \boldsymbol{\alpha}) s(x) \end{aligned}$$

since $s(a) = 0$ for $a \in A$. Thus,

$$\begin{aligned} \mathrm{E}\left[\sum_{t=0}^{\infty} s(X_t)\right] &= \sum_{t=0}^{\infty} \boldsymbol{\alpha} Q^t \boldsymbol{s}^T \\ &= \boldsymbol{\alpha}\left(\sum_{t=0}^{\infty} Q^t\right)\boldsymbol{s}^T \\ &= \boldsymbol{\alpha}(I-Q)^{-1}\boldsymbol{s}^T \end{aligned} \tag{3.12}$$

using Appendix C and where I denotes the $|\Omega \setminus A|^2$ identity matrix.

3.10.2 A chain binomial example

In order to demonstrate the implementation of the above theory to a discrete time epidemic model featuring a delay before intervention, a chain binomial model of the Reed-Frost type (with geometric infectious and removed periods) will be used. For more information on chain binomial models see Gani and Jer-

wood (1971). Let S_t, I_t, R_t and V_t denote the number of susceptible, infective, removed and response individuals respectively at time t in the epidemic, for $t = 0, 1, \ldots$. Assume (S_0, I_0, R_0, V_0) is known, then for $t = 0, 1, \ldots$, recursively define the epidemic as follows. Given S_t, I_t, R_t, V_t, define

$$\begin{aligned} S_{t+1} &\sim \text{Bin}(S_t, q^{I_t}), \\ I_{t+1} &\sim S_t - S_{t+1} + \text{Bin}(I_t, \theta_I), \\ R_{t+1} &\sim S_t - S_{t+1} + I_t - I_{t+1} + \text{Bin}(R_t, \theta_R), \\ V_{t+1} &= S_t + I_t + R_t + V_t - S_{t+1} - I_{t+1} - R_{t+1}. \end{aligned}$$

where $\text{P}(\text{Bin}(n, p) = k) = \binom{n}{k} p^k (1-p)^{n-k}$ for $k = 0, \ldots, n$. Since this model has the Markov property, the infectious and removed periods have geometric distributions with means of $(1-\theta_I)^{-1}$ and $(1-\theta_R)^{-1}$ respectively.

The form of the transition matrix P depends upon the size of the state space and this is determined by the initial conditions. When $(S_0, I_0, R_0, V_0) = (1, 1, 0, 0)$ this Markov process (so far without intervention) has transition matrix

$$\begin{array}{c} \\ 110 \\ 020 \\ 011 \\ 010 \\ \mathbf{0} \end{array} \begin{array}{c} \begin{array}{ccccc} 110 & 020 & 011 & 010 & \mathbf{0} \end{array} \\ \begin{bmatrix} q\theta_I & (1-q)\theta_I & (1-q)(1-\theta_I) & 0 & q(1-\theta_I) \\ 0 & \theta_I^2 & 2\theta_I(1-\theta_I) & 0 & (1-\theta_I)^2 \\ 0 & 0 & \theta_I\theta_R & \theta_I(1-\theta_R) & 1-\theta_I \\ 0 & 0 & 0 & \theta_I & 1-\theta_I \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

where state abc has $(S_t, I_t, R_t, V_t) = (a, b, c, 2-a-b-c)$ and state $\mathbf{0}$ is the pooled absorbing state (i.e. states with zero infectives). If we now implement

the intervention $v = 1$, transitions involving an individual leaving the removed category and entering the response category (e.g. $011 \rightarrow 010$) now go to the absorbing state $\mathbf{0}$ instead. The transition matrix P becomes

$$\begin{array}{c} \\ 110 \\ 020 \\ 011 \\ \mathbf{0} \end{array} \begin{array}{c} \begin{array}{cccc} 110 & 020 & 011 & \mathbf{0} \end{array} \\ \begin{bmatrix} q\theta_I & (1-q)\theta_I & (1-q)(1-\theta_I) & q(1-\theta_I) \\ 0 & \theta_I^2 & 2\theta_I(1-\theta_I) & (1-\theta_I)^2 \\ 0 & 0 & \theta_I\theta_R & 1-\theta_I\theta_R \\ 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

since it is no longer possible to enter the state 010 without triggering the intervention.

To apply equation (3.12), we need the submatrix of the transition matrix for the non-absorbing states, called Q. In this example Q is the upper-left 3×3 submatrix of the transition matrix P. We also need the initial distribution ($\boldsymbol{\alpha} = (1, 0, 0)$) and the vector $\boldsymbol{s}$. Since we are calculating the expected value of the effective severity of the epidemic $\sum_{t=0}^{T_1} I_t$, we require $s(\boldsymbol{x})$ to give the number of infectives in state $\boldsymbol{x}$ and therefore in this example, $\boldsymbol{s} = (1, 2, 1)$. Thus the expected effective severity χ generated by this epidemic is,

$$\begin{aligned} \chi &= \mathrm{E}\left[\sum_{t=0}^{T_1} I_t\right] \\ &= \boldsymbol{\alpha}(1-Q)^{-1}\boldsymbol{s}^T \\ &= \frac{1}{1-q\theta_I}\left(1 + \frac{2\theta_I(1-q)}{(1-\theta_I)} - \frac{(1-3\theta_I^2)(1-q)}{(1-\theta_I\theta_R)(1+\theta_I)}\right). \end{aligned}$$

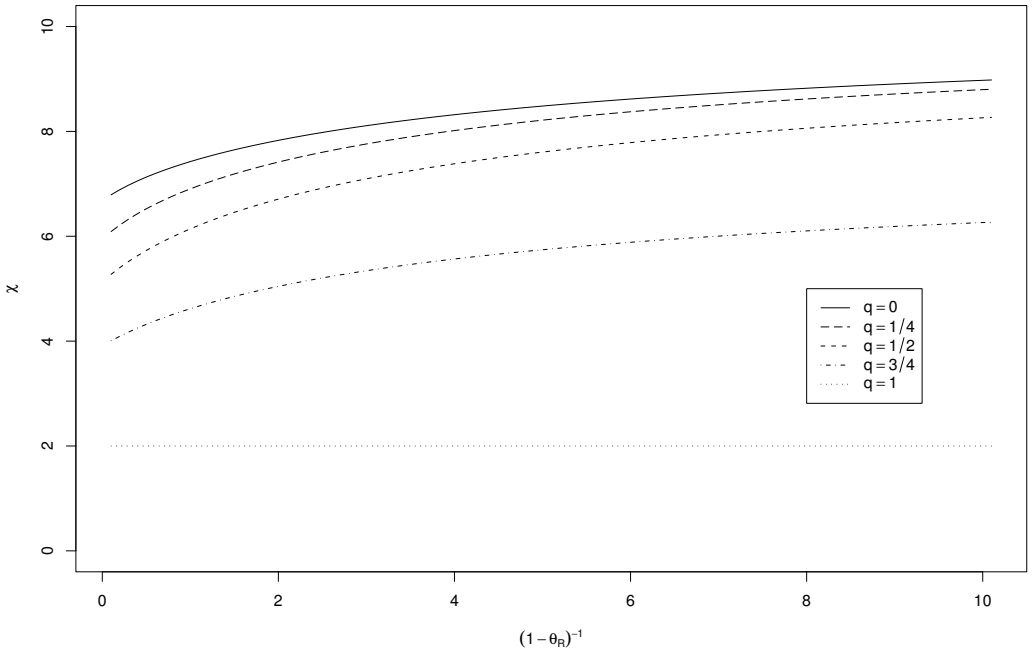

Figure 3.21: The expected effective severity χ against the expected removed period $(1-\theta_R)^{-1}$ with $n = 4$, $i = v = 1$ and $\theta_I = 0.5$.

Effects of parameter changes

Figure 3.21 demonstrates the effect of increasing the expected removed period in a larger household of five individuals, assuming the same chain binomial epidemic model. Several values of the probability a given susceptible avoids infection from a given infective in one time unit (q) are given in order to demonstrate the effect of varying the disease's infectiousness. The expected infectious period is defined to be two time units instead of one, in order to allow the possibility that infectives are not instantly removed. When $q = 1$, no further individuals can become infected and so the expected effective severity χ is simply that generated by the initial infective. However, once q is reduced below one, increasing the expected removed period increases χ.

When $q = 0$, all of the initial susceptibles are infected at the first time unit. The expected severity generated without the intervention is therefore ten, and we can see that even with the shortest possible removed period (one time unit), χ is only reduced by about a third. This can be explained as follows. Of all possible paths the epidemic can take, the lowest possible value of χ is five since the intervention cannot occur before time two. In all other paths the intervention occurs later and therefore even more severity may be generated.

Overall, this model appears to be quite robust to changes in the expected removed period. This is because all of the individuals infected before the intervention experience infectious periods of at least one time unit, still half of their expected length. In the continuous time model, infectious periods may be cut off almost instantly, and therefore when the number of infectives is high, an intervention has more effect for this model. In practice, it may be difficult to cut short infectious periods once they have started and so the discrete time model may be more realistic in this respect.

3.10.3 Application to realistic parameter values.

Longini *et al.* (2004) use a discrete time epidemic model in order to predict the effectiveness of several different interventions on an outbreak of pandemic influenza in a fixed population of 2000 individuals representing a small American town. Their model includes six types of infective and four levels of mixing. Due to the complexity of their model they are unable to calculate R_* and instead estimate a threshold parameter by simulation. After simplifying the model somewhat, it becomes possible to calculate R_* using the discrete time method described above.

Ball and Lyne (2001) state that for a multitype epidemic model with two levels of mixing, R_* is given by the largest eigenvalue of the matrix of mean offspring M, where

$$m_{i,j} = \sum_{\boldsymbol{h}} \alpha_i(\boldsymbol{h}) \sum_k \mathrm{E}[T_k^A | \boldsymbol{h}, i] \lambda_{k,j}, \tag{3.13}$$

and where $\alpha_i(\boldsymbol{h})$ is the probability that a type i individual chosen uniformly at random resides in a household of configuration $\boldsymbol{h}$; $\lambda_{k,j}$ is the rate at which a type k individual globally contacts a type j individual; and $(T_k^A | \boldsymbol{h}, i)$ is the sum of the infectious periods of the type j individuals in a household of configuration $\boldsymbol{h}$ (ignoring global contacts), given that the subepidemic within that household was started by a single individual of type i.

In order to apply this formula for R_* with two levels of mixing to the model of Longini *et al.* (2004), it needs to be simplified. This is done by incorporating the two intermediate levels of mixing (neighbourhood contacts and school contacts) into the global mixing, in such a way that the expected number of outside contacts made by a given infective over their infectious period remains unchanged. For simplicity, the six types of individual used by Longini *et al.* (adults and five ages of children) have been reduced to two types (adults and children). This is unlikely to make much difference to R_* as the expected number of infectious contacts a day made by the five types of infected children are mostly very similar. In the paper, every type of individual has the same latent and infectious period distribution with means of 1.9 days and 4.1 days respectively. Using the method outlined here (without an intervention), the matrix of mean offspring

M is given by

$$\begin{bmatrix} m_{a,a} & m_{a,c} \\ m_{c,a} & m_{c,c} \end{bmatrix} = \begin{bmatrix} 0.32 & 0.37 \\ 0.28 & 3.13 \end{bmatrix},$$

which implies that $R_* = 3.17$. Longini *et al.* (2004) estimate R_0 to be 1.67 by repeatedly selecting an individual in the population at random and counting the number of infections they produce during their infectious period in an otherwise susceptible and non-infectious population. It is also possible to estimate R_* using the same technique - select an individual at random and calculate the average number of *households* infected either by the initial infective or by any other members of their household. This method estimates R_* to be 1.82.

Clearly there is a large discrepency between the calculated value for the approximate model and the simulated values for R_0 and R_*. Further investigation reveals that the calculated and simulated values for R_* agree very closely when the school level of mixing is removed from the simulations and the global rate of mixing in the calculation is adjusted accordingly.

An explanation of this is as follows. The theoretical value of R_* (the largest eigenvalue of the matrix of mean offspring) gives an indication of the long-term behaviour of the branching process approximation to the epidemic model. Because the matrix of mean offspring relates to the branching process, the entry $m_{i,j}$ does not explicitly depend upon the number of households of each type, only those containing type i individuals (see the definition of $\alpha_i(\boldsymbol{h})$ in equation (3.13)). Clearly the simulation method does explicitly depend upon this, and when one type of individual is many times more infectious than the others and is also a small minority of the population, then the theoretical R_* will be large

(the infection will be propagated in the minority group) however the simulated values of R_0 and R_* are much smaller, as the initial infective will be chosen from the minority group in only a very small proportion of the realisations. This implies that the 'true' value of R_* is probably much closer to the value calculated for the approximate model than the value given in the paper.

With intervention

Longini *et al.* (2004) consider a series of complex interventions with antiviral prophylaxis for up to eight weeks for traced contacts of symptomatic cases. They assume that not only does prophylaxis reduce the susceptibility, infectiousness and probability of developing symptomatic illness if infected, it additionally reduces the length of the infectious period by 1 day. Also, some vaccination based strategies are considered. Since these types of intervention are difficult to include in the calculation of R_*, we will continue with the household based intervention considered in the rest of this chapter (with $v = 1$), namely, that when an individual is detected at the end of their infectious period, T_R days pass before their household is isolated from all of its external mixing groups and makes no further infectious contacts. For their more complex interventions, Longini *et al.* (2004) conclude that for an intervention delay of between three and five days whilst there is still a significant reduction in the numbers of cases and deaths, the probability of a major epidemic (which they define as an overall attack rate greater than 2.5%) is largely unaffected by the intervention.

We consider two types of intervention, the (more realistic) weak type where only symptomatic individuals can trigger an intervention and the strong type

where any infectious individual can trigger the intervention. Table 3.3 shows the values of R_* for the approximate models with weak and strong interventions for different values of T_R.

T_R	R_* (strong)	R_* (weak)
0	2.164	2.404
1	2.182	2.416
2	2.198	2.430
3	2.210	2.441
4	2.219	-
∞	3.172	3.172

Table 3.3: The effect of increasing the delay before intervention T_R on R_* for two kinds of intervention.

Neither of the two types of intervention considered are successful in reducing the threshold parameter R_* to below one. Also, there appears to be very little drop in the effectiveness of the intervention as the delay is increased from zero to three, unlike the Longini finding. When the delay is infinite, no intervention occurs and so the row for infinity gives R_* without intervention. In fact, this could be relabelled $T_R = 63$, as the longest time the epidemic can last is the maximum serial interval (the gap between being infected and infecting others) multiplied by the number of individuals in the household. If R_* is concave in T_R, which is reasonable, the values in the table do not approach R_* without intervention rapidly enough to reach it by $T_R = 63$. A likely reason for this is the accumulation of truncation errors as T_R is increased, as the state space increases in size to more than one million states by $T_R = 4$.

3.11 Conclusion and Extensions

This chapter has used an epidemic model to analyse the effect of a delay before an intervention can be applied. The length of this delay between the end of the infectious period and the triggering of the intervention was called the removed period. The effectiveness of the intervention was quantified by the reduction in the threshold parameter R_*, which is proportional to the expected effective severity (the sum of the infectious periods until intervention). In general, the findings agreed with the papers by Longini *et al.* (2004) and Eubank *et al.* (2004) - the effectiveness of an intervention rapidly decreases as the delay increases. However, when the model used by Longini *et al.* (2004) was approximated this finding was not replicated, probably due to the accumulation of truncation errors. In the case of the epidemic model, we have seen that this reduction in effectiveness can be mitigated somewhat by the addition of latent periods.

A second important finding was that for the households model the reproduction number was quite robust to changes in the within household infection rate. Since this parameter is difficult to estimate accurately in practice, a very useful upper bound on R_* can be obtained by letting the within household transition rate be infinite. This implies that as soon as the first member of a household reaches their infectious period, the whole household is infected. When the two types of delay period distribution were compared, we saw that the constant delay creates more severity than the exponential delay, when the intervention is applied after the first observation, however if large numbers of observations are required to trigger the intervention this trend is reversed.

When a supercritical branching process version of the model is considered, an

early intervention is again very important, because the number of infectives can quickly become very large. Discrete time versions of the model were also studied, including a chain binomial model similar to the continuous time epidemic model. For the chain binomial model the intervention appeared to be less effective, because infectious periods could not be shortened by as much by the intervention as in the continuous time case.

Although the model considered in this chapter is quite general, progress has only been made in the continuous time setting for some specific removed period distributions (the constant and exponential) and exponentially distributed infectious and latent periods. Clearly these distributions are not always appropriate, particularly for human diseases, and so more distributions could be considered. In practice temporal data for epidemics is usually in the form of case numbers per day and so parameter estimation is likely to be more straightforward for a discrete time model, and a quite general approach is developed for these models.

Chapter 4

Evaluating the probability of containment for pandemic influenza

4.1 Introduction

Strains of the influenza A virus (for example H5N1) are thought to be extremely likely to cause the next major pandemic (Mills *et al.*, 2006; Ferguson *et al.*, 2005). Interventions and control measures aimed at reducing the spread of the virus will be applied to any area where a highly pathogenic strain emerges. This chapter aims to develop techniques to assess the probability that, despite being eradicated from the area in which the infection emerged, the virus escapes to other areas where surveillance and interventions might not be in place. To this end, a model is constructed for the spread of the influenza virus that includes transmission events which allow the disease to escape from the modelled

population. The probability that one of these escape events does not occur is then derived.

4.1.1 Chapter structure

This chapter is structured as follows. Firstly this introductory section discusses the modelling issues surrounding influenza pandemics. Section 4.2 defines the model in as much generality as possible, before deriving the probability that the epidemic is successfully contained within the population. Next, section 4.3 considers some simplifications of the model in order to demonstrate the effect on the probability of containment of the basic parameters. These simplifications include the case in which all of the households are equally infectious with known infectious offspring distribution, then a model for the household subepidemics (without intervention) is explored. Following this we consider the effect of including different sized households in the model, and a simple model with different types of infectious individuals is explored - all without interventions. In section 4.4 the effect of the shape of the infectious period distribution on the containment probability is explored, and found to depend upon the Laplace transform of the household severity distribution. Household based interventions are introduced in section 4.5, firstly using a Markov process to model the within household epidemics and then a simulation model is used to predict the household severities.

4.1.2 Influenza

This section describes some features of the influenza virus and the H5N1 subtype in particular, which suggest that it may cause a global pandemic.

The influenza A virus is constantly changing through a process called antigenic drift. In this process random genetic mutations give rise to new strains, which then undergo intense selection pressure caused by competition with similar strains of the influenza virus, and the ability of their host population to develop immunity to particular influenza strains (Ferguson and Anderson, 2002). Such a mechanism is considered unlikely to cause a global pandemic as there is evidence to suggest that infection by a particular strain of influenza A gives the host partial immunity to closely related strains of the virus, thus reducing the transmissibility of emerging strains (Casagrandi *et al.*, 2006). However, the influenza A viruses circulating amongst humans can also undergo sudden genetic changes by experiencing antigenic shift. This is where a new influenza A subtype is introduced into the human population, for instance directly from animal populations or through a reassortment event. Reassortment events can occur in an intermediate host (for example swine) or in humans when they are co-infected with two quite different strains of influenza A. Genetic material from the two viruses can mix during viral replication (Brown *et al.*, 1998). In the past, antigenic shifts have corresponded to the emergence of novel strains of influenza A which have gone on to cause severe pandemics, for example the Spanish flu epidemic in 1918 (Casagrandi *et al.*, 2006).

Subtypes of the influenza virus are categorised by two types of protein spikes protruding through their lipid outer membrane. There are 15 known types

of haemagglutinin (H) and 9 known types of neuroaminidase (N) in mammals and birds. The H5N1 subtype is currently thought most likely to cause a global pandemic, as this subtype is highly prevalent in both domesticated and wild bird populations (Mills *et al.*, 2006), giving rise to the terms avian influenza and bird flu. H5N1 is the first subtype with the H5 protein to be able to infect humans, and so human populations have little pre-existing immunity (Buxton Bridges *et al.*, 2000). Fortunately, it currently lacks the ability for efficient transmission between humans, as evidenced by the recent outbreaks in Asia (WHO, 2007).

Since it is impossible to predict the exact strain of influenza that will cause a pandemic, the production of a pandemic-preventing vaccine is difficult. Currently, the seasonal influenza A vaccine is produced using hens' eggs ordered six months in advance and so production cannot suddenly be increased (Oxford, 2006). The first line of defence against an emerging strain is antiviral prophylaxis. It has been shown that these drugs can reduce the duration of symptomatic illness and that by administering antivirals to a household after the identification of an index case, the spread in the family can be reduced by more than 80%. (Welliver *et al.*, 2001).

4.1.3 Modelling pandemic influenza

This section discusses some features that may be important to include in a model for the spread of an emerging strain of influenza through a human population.

Mathematical modelling has suggested that it may be possible to contain an

outbreak of an emergent pandemic strain of influenza using a combination of antiviral prophylaxis and social distancing measures, if the intervention is applied in the very early stages (Ferguson *et al.*, 2005). However this paper focuses on a particular region of Southeast Asia, and does not consider the possibility that the disease may be transported outside of this region to an area where the infection controls and disease surveillance may not be in place. Although such infectious contacts may be considerably less likely than local contacts and even country-wide contacts, the mass availability of international travel means that the effects of such contacts could be devastating and should not be ignored. An example of this kind of global contact occurred during the SARS outbreak of 2002/3, when a couple from Toronto spent ten days in Hong Kong before returning to Canada to trigger a second epidemic (Booth *et al.*, 2003).

When modelling the spread of influenza through a sizable human population, it is usually important to include the following features in the model. Firstly, the population should be stratified by age as past pandemics have shown that one particular age-group may be more at risk than others. In 1918 mainly 25-35 year-olds were at risk, however, when H1N1 re-emerged in 1977 under 25 year-olds were at risk, as they had no prior immunity obtained from the virus's circulation in the 1950's, (Oxford, 2006). Influenza is also well known to cause asymptomatic or mildly symptomatic infections in a proportion of the people it infects (Kaiser *et al.*, 2000). This makes the infection harder to track and to detect. Finally it is important to note that since transmission occurs through close contacts, infectious contacts are likely to be made to relatives or colleagues.

4.1.4 Modelling interventions

There are several ways in which interventions can be included in a model, each appropriate to different kinds of real-life interventions. In practice, a combination of interventions are likely to be used in order to give the best chance of reducing the reproduction number of the epidemic to below one with minimal disruption and expense. The easiest way to model an intervention is to allow the rate at which infectious contacts occur to reduce over time. This is appropriate when the mixing behaviour of the population changes, for instance when only essential journeys are undertaken; mass vaccination or antiviral prophylaxis are used to reduce susceptibility; face masks are worn in public places (as happened during the SARS epidemic in 2002/3, see for example Lau *et al.*, 2004); or handwashing and other types of disinfection are increased.

Interventions may be included in a model at the household level by incorporating a trigger into the within household subepidemic after which the behaviour in the household changes, for example susceptibility and infectiousness could decrease or infectious periods could be reduced. This method is suitable for clinical interventions, such as treatment with antivirals to reduce infectivity and to shorten the infectious periods, as well as a policy of isolating household members to reduce contact rates. This kind of intervention is the main subject of this chapter.

Finally, contact tracing interventions can be applied, in which an infective identifies any individuals which they have may infected (forward tracing) or any individuals that may have infected them (backward tracing). These traced contacts are then are pre-emptively treated with antivirals or isolated, and have

their contacts traced also. This kind of intervention can be difficult to include realistically in the model, as in practice there is often a limit to the treatment capacity of the health services. Some papers that consider contact tracing interventions include Muller *et al.* (2000), Eubank *et al.* (2004) and Kaplan *et al.* (2004).

4.1.5 Assessing the probability of containment

This section sets out the objective of this chapter of the thesis, and briefly describes how it will be achieved.

The aim of this chapter is to assess the probability that despite being successfully eliminated from an outbreak area, a potentially pandemic-causing strain of the influenza virus escapes the area where it initially emerged to cause further outbreaks elsewhere. This will be achieved by developing a model for the spread through a population of an emerging strain of influenza constrained by interventions, and then considering additional contacts to individuals external to the outbreak population. A branching process of households will be used to model the spread of infection through the population in the outbreak region, and a Poisson process will be used to model infectious contacts to individuals external to this population.

4.2 The general model

In this section the model is defined in full generality, and the probability of containment is derived.

4.2.1 Definition of the model

This section describes a continuous time multitype epidemic model with two levels of mixing, with additional external contacts that allow the disease to escape from the population. The branching process approximation is then applied to this model in order to make it more tractable. Finally, it is noted that in order to calculate the probability of containment, it suffices to work with the discrete time branching process embedded within this continuous time branching process model.

Consider a finite closed population of several types of individual, partitioned into a large number of households. This population is called the internal population. At this stage the model is kept as general as possible for flexibility. At some point after being infected individuals undergo an infectious period. During this period they can make three types of infectious contact. Firstly, they can infect other members of their household. It is not necessary to specify a model for within household transmission at this point - this allows different models for household based interventions to be introduced later. Secondly, an infective can make an infectious contact to an individual in another household in the internal population, and we assume that such contacts are made at the points of a Poisson process with rate dependant on the types of the two individuals. Finally, an infective can make an infectious contact to an individual outside the

internal population, termed an external contact. It is assumed that individuals make external contacts at the points of a Poisson process with rate dependent on the type of infective. When an individual's infectious period is over, they can make no more infectious contacts and they cannot be re-infected. We assume the Poisson processes describing internal contacts and external contacts are all mutually independent.

In order to make this model more tractable, consider its branching process approximation by letting the number of households tend to infinity. We scale the rates in the Poisson processes governing transmissions between individuals of different households by the size of the population, so that the average number of contacts made by each type of infective to each type of individual in other households remains unchanged as the population size becomes infinite. Thus, we have obtained the branching process approximation to the epidemic model described above, where the 'individuals' in the branching process correspond to household subepidemics. The type of these 'individuals' in the branching process is specified by both the composition of individuals in the household and the type of the initial infective in the household subepidemic. For example, a household containing two adults and one child creates two types of household subepidemic: one instigated by an adult and another instigated by the child. A household containing only two adults creates a third type of subepidemic. This branching process approximation is valid for the early stages of an outbreak when the probability that an infectious individual contacts an individual in a household already affected by the epidemic is negligible.

Next, notice that since we are interested in the probability that there are no external contacts over all time, the temporal information contained in the model

is irrelevant. It therefore suffices to consider the discrete time branching process embedded within this continuous time branching process, obtained by simply counting the number of each type of infected household in each generation of the infection.

For $1 \leq k \leq K$ and $1 \leq h \leq H$, define the random variable $S_{h,k}$ to be the sum of the type k infectious periods in a household subepidemic of type h. This random variable is called the type k severity produced by a type h household subepidemic. If there are I types of individual in the epidemic model we started out with, then $K \leq I$ is defined to be the smallest number of severity types needed to correctly describe the embedded discrete time branching process. If there are J arrangements of these I types of individual into households in the original epidemic model, $H \leq IJ$ is defined to be the smallest number of household subepidemic types needed to correctly describe the discrete time branching process. Notice that in general the severity distribution of these subepidemics will depend on the type of the initial infective. It is often possible to use fewer types of severity than types of individual as any two types of individual that make external contacts at the same rate and instigate each type of household subepidemic at the same rate can be considered to produce the same type of severity. Note that they do not necessarily need to have the same infectious period distribution or household contact rates.

For example, assume every household contains two adults and two children each making external contacts at rate 1, internal contacts to adults at rate 2 and internal contacts to children at rate 3, but with different infectious period distributions and household contact rates. Since infectious contacts originate from adults and children at the same rate, just one type of severity is needed ($K = 1$).

However, adults and children are contacted at different rates (and have different infectious period distributions) and so two household subepidemics are required ($H = 2$), one initiated by each type of individual. If infected, adults and children will contribute different amounts to the household's severity, as they have different infectious periods.

Similarly the number of household subepidemic types can often be reduced from IJ, for instance when not every type of infective is in every household arrangement.

For $1 \leq k \leq K$ and $1 \leq u \leq H$, define $\beta_{k,u}$ to be the rate at which type u household subepidemics are produced from type k severity and define the number of household subepidemics of type u generated by a household subepidemic of type h to be $X_{h,u}$. Thus, in the H-type discrete time branching process an individual of type h produces $X_{h,u}$ offspring of type u and we have that

$$X_{h,u} \sim \text{Pois}\left(\sum_{k=1}^{K} S_{h,k}\beta_{k,u}\right).$$

For $1 \leq k \leq K$, define α_k to be the rate at which individuals producing type k severity make external contacts. Therefore, a household with severity distribution $\boldsymbol{S}_h = (S_{h,1}, \ldots, S_{h,K})$ produces a number of external contacts with a Poisson distribution with mean $\sum_{k=1}^{K} S_{h,k}\alpha_k$. Let $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_K)$, for $1 \leq h \leq H$ let $\boldsymbol{\beta}_h = (\beta_{1,h}, \ldots, \beta_{K,h})$ and for $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_K) \in [0, \infty)^K$ define

$$\psi_h(\boldsymbol{\theta}) = \text{E}\left[\exp\left\{-\sum_{k=1}^{K} \theta_k S_{h,k}\right\}\right].$$

Finally, for $1 \leq h \leq H$ and $1 \leq k \leq K$, define $\Delta_{h,k}$ to be the sum of the type k severity generated throughout the entire course of a branching process started

from one household subepidemic of type h, and write $\boldsymbol{\Delta_h} = (\Delta_{h,1}, \ldots, \Delta_{h,K})$.

4.2.2 The threshold parameter

This section discusses the threshold parameter for the branching process of households used as a model.

Let M be the matrix of mean offspring, so for $1 \leq i, j \leq H$, $m_{i,j}$ is the expected number of type j household subepidemics to emanate from a type i household subepidemic. In our branching process model, conditional on the severity vector of the type i household subepidemic $\boldsymbol{S}_i$, the number of type j household subepidemic offspring has a Poisson distribution with mean $\boldsymbol{S}_i.\boldsymbol{\beta}_j$. Thus, M is the product of two rectangular matrices, $M = SB$. The $H \times K$ matrix S has at the (h,k)th entry the expected type k severity of a type h household, and the $K \times H$ matrix B has at the (k,h)th entry the rate at which a type k infectious individual infects type h households.

Branching process theory tells us that there is a reproduction number R which dictates the ultimate behaviour of the process. If the matrix of mean offspring M is positive regular (for some $n \in \mathbb{N}$, every entry of M^n is positive) then R is equal to the largest eigenvalue of M. If $R > 1$, there is a positive probability that the branching process will have infinite total progeny, and if $R \leq 1$ the number of offspring will be almost surely finite. However, if $R \geq 1$ the expected severity of the branching process will be infinite, and finite if $R < 1$; as the expected time taken for the branching process to die out is infinite for $R = 1$, despite the fact that extinction is certain. For more information about the threshold parameter of a branching process see for example Mode (1972) and

Jagers (1975).

Ball *et al.* (1997) have a slightly different definition of the threshold parameter for a multitype epidemic model with two levels of mixing. They use the reproduction number for a branching process approximation to the epidemic process to provide a reproduction number for the epidemic process (which has finite population), so it is also relevant here. Instead of considering the expected number of new infectious households created from an infectious household, they consider the expected number of infectious individuals outside of an initial infective's household to be created by an initial infective and *the other members of their household*. Thus, if there are K infectious types, they form a $K \times K$ matrix M^* in which $m^*_{i,j}$ is the expected number of type j infectives to be globally infected from a household subepidemic started by a type i infective. Call the largest eigenvalue of this matrix R_*.

For our model, $M^* = BS$, where B and S are as before. The number of household types H must be greater than or equal to the number of infectious types K since a susceptible household that contains two types of individual forms two infectious household types, with each infectious household type corresponding with the initial infective's type. Thus, the matrix M^* is a more compact representation of the same information contained in M. Theorem A.6.2 of Mardia *et al.* (1979) states that for any two matrices X and Y with dimension $n \times m$ and $m \times n$ respectively, the non-zero eigenvalues of XY and YX are the same and have the same multiplicity. The threshold parameters R and R_* are therefore equal.

4.2.3 Derivation of the containment probability

The probability of containment is defined to be the probability that there are no external contacts throughout the entire course of the branching process. Individuals producing severity of type k ($1 \leq k \leq K$) make external contacts at rate α_k. Thus, for $1 \leq h \leq H$, given the total severity vector $\boldsymbol{\Delta}_h$ of a branching process initiated by a single household subepidemic of type h, the probability of no external contacts throughout the whole branching process is $\exp(-\boldsymbol{\alpha}.\boldsymbol{\Delta}_h)$. Thus,

$$\mathrm{P}(\text{containment}|h) \;=\; \mathrm{E}[\exp(-\boldsymbol{\alpha}.\boldsymbol{\Delta}_h)],$$

i.e. the containment probability of a branching process starting from one infectious household of type h is the joint generating function of the total severity created by such branching process, evaluated at $\boldsymbol{\alpha}$. Let G_h be this generating function, so that

$$G_h(\boldsymbol{\theta}) \;=\; \mathrm{E}[\exp(-\boldsymbol{\theta}.\boldsymbol{\Delta}_h)]$$

for $1 \leq h \leq H$ and $\boldsymbol{\theta} \in [0,\infty)^K$, and so the probability of containment is given by $G_h(\boldsymbol{\alpha})$.

Theorem 4.1 *For $h \in \{1,\ldots,H\}$, the $G_h(\boldsymbol{\theta})$ satisfy the equations*

$$G_h(\boldsymbol{\theta}) = \psi_h\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - G_u(\boldsymbol{\theta}))\boldsymbol{\beta}_u\right). \tag{4.1}$$

Proof:

Let $X_{h,u}$ be the number of type u infectious households created by the initial type h infectious household. Firstly notice that a branching process can be written in terms of the zeroth generation combined with independent copies of the branching process, each started by an individual from the first generation of the original branching process. For instance, the total severity satisfies

$$\boldsymbol{\Delta}_h = \boldsymbol{S}_h + \sum_{u=1}^{H} \sum_{j=1}^{X_{h,u}} \boldsymbol{\Delta}_u^{(j)}$$

where the $\boldsymbol{\Delta}_u^{(j)}$ are independent and identically distributed copies of $\boldsymbol{\Delta}_u$ and the empty sum is zero. This implies that

$$\begin{aligned}
G_h(\boldsymbol{\theta}) &= \mathrm{E}[\exp(-\boldsymbol{\theta}.\boldsymbol{\Delta}_h)] \\
&= \mathrm{E}\left[\exp\left(-\boldsymbol{\theta}.\left(\boldsymbol{S}_h + \sum_{u=1}^{H}\sum_{j=1}^{X_{h,u}} \boldsymbol{\Delta}_u^{(j)}\right)\right)\right] \\
&= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}_h}\left(\prod_{u=1}^{H} \exp\left(\sum_{j=1}^{X_{h,u}} -\boldsymbol{\theta}.\boldsymbol{\Delta}_u^{(j)}\right)\right)\right] \\
&= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}_h}\left(\prod_{u=1}^{H} G_u(\boldsymbol{\theta})^{X_{h,u}}\right)\right] \\
&= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}_h}\mathrm{E}\left[\prod_{u=1}^{H} G_u(\boldsymbol{\theta})^{X_{h,u}}\middle|\boldsymbol{S}_h\right]\right] \\
&= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}_h}\prod_{u=1}^{H}\exp\left\{-(\boldsymbol{\beta}_u.\boldsymbol{S}_h)(1-G_u(\boldsymbol{\theta}))\right\}\right]
\end{aligned}$$

since conditional on $\boldsymbol{S}_h$, the $X_{h,u}$ are independent Poisson-distributed random variables with means $\boldsymbol{\beta}_u.\boldsymbol{S}_h$, for $u = 1, \ldots, H$. Thus,

$$\begin{aligned} G_h(\boldsymbol{\theta}) &= \mathrm{E}\left[\exp\left\{-\left[\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - G_u(\boldsymbol{\theta}))\boldsymbol{\beta}_u\right].\boldsymbol{S}_h\right\}\right] \\ &= \psi_h\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - G_u(\boldsymbol{\theta}))\boldsymbol{\beta}_u\right). \end{aligned}$$

4.2.4 Uniqueness

In this section the number of solutions to equations (4.1) is discussed. For convenience, rewrite equations (4.1) as

$$G_h = f_h(\boldsymbol{G}),$$

for $1 \leq h \leq H$, where $\boldsymbol{G} = (G_1, \ldots, G_H)$ are the generating functions with their $\boldsymbol{\theta}$ dependence suppressed and for $\boldsymbol{x} = (x_1, \ldots, x_H) \in [0, 1]^H$,

$$f_h(\boldsymbol{x}) = \psi_h\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - x_u)\boldsymbol{\beta}_u\right).$$

First a lemma is needed.

For $1 \leq u, h \leq H$ and $t = 0, 1, \ldots$, let $Z_{h,u}(t)$ be the number of type u individuals in generation t of a branching process with generation zero consisting of a single type h individual. For $1 \leq h \leq H$, $1 \leq k \leq K$ and $t \in \mathbb{N}$, let the cumulative severity $\Delta_{h,k}(t)$ be the sum of the type k severity generated by the first $t - 1$ generations of the branching process described above, with the convention $\Delta_{h,k}(0) = 0$. Form the vectors $\boldsymbol{Z}_h(t) = (Z_{h,1}(t), \ldots, Z_{h,H}(t))$

and $\boldsymbol{\Delta}_h(t) = (\Delta_{h,1}(t), \ldots, \Delta_{h,K}(t))$. For $1 \leq h \leq H$ and $t = 0, 1, \ldots$, let $f_h^t(\boldsymbol{x}) = \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h(t)}\boldsymbol{x}^{\boldsymbol{Z}_h(t)}\right]$ where the notation $\boldsymbol{x}^{\boldsymbol{y}}$ for H-vectors $\boldsymbol{x}$ and $\boldsymbol{y}$ is defined by

$$\boldsymbol{x}^{\boldsymbol{y}} = \prod_{h=1}^{H} x_h^{y_h}.$$

Finally, let $\boldsymbol{f}^t(\boldsymbol{x}) = (f_1^t(\boldsymbol{x}), \ldots, f_H^t(\boldsymbol{x}))$.

Lemma 4.2 *For $t \in \mathbb{N}$ and $\boldsymbol{x} \in \mathbb{R}^H$,*

$$f_h^t(\boldsymbol{x}) = f_h(\boldsymbol{f}^{t-1}(\boldsymbol{x})). \tag{4.2}$$

Proof:

$$\begin{aligned} f_h^t(\boldsymbol{x}) &= \mathrm{E}[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h(t)}\boldsymbol{x}^{\boldsymbol{Z}_h(t)}] \\ &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\left(\boldsymbol{S}_h + \sum_{u=1}^{H}\sum_{j=1}^{X_{h,u}} \boldsymbol{\Delta}_u^{(j)}(t-1)\right)} \boldsymbol{x}^{\sum_{u=1}^{H}\sum_{j=1}^{X_{h,u}} \boldsymbol{Z}_u^{(j)}(t-1)}\right] \end{aligned}$$

where $X_{h,u}$ is the number of type u offspring from the type h ancestor and the $\boldsymbol{\Delta}_u^{(j)}(t-1)$ and the $\boldsymbol{Z}_u^{(j)}(t-1)$ are i.i.d. copies of the random vectors $\boldsymbol{\Delta}_u(t-1)$ and $\boldsymbol{Z}_u(t-1)$ respectively. So,

$$\begin{aligned} f_h^t(\boldsymbol{x}) &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}_h}\prod_{u=1}^{H}\left(e^{\sum_{j=1}^{X_{h,u}} -\boldsymbol{\theta}.\boldsymbol{\Delta}_u^{(j)}(t-1)} \boldsymbol{x}^{\sum_{j=1}^{X_{h,u}} \boldsymbol{Z}_u^{(j)}(t-1)}\right)\right] \\ &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}_h}\prod_{u=1}^{H}\left(e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_u^{(1)}(t-1)}\boldsymbol{x}^{\boldsymbol{Z}_u^{(1)}(t-1)}\right)^{X_{h,u}}\right] \end{aligned}$$

since the $\boldsymbol{\Delta}_u^{(j)}(t-1)$ and the $\boldsymbol{Z}_u^{(j)}(t-1)$ are independent of each other and of

$\boldsymbol{S}_h$ and $\boldsymbol{X}_h = (X_{h,1}, \ldots, X_{h,H})$. Thus,

$$\begin{aligned} f_h^t(\boldsymbol{x}) &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}_h} \prod_{u=1}^{H} f_u^{t-1}(\boldsymbol{x})^{X_{h,u}} \right] \\ &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}_h} \mathrm{E}\left[\prod_{u=1}^{H} f_u^{t-1}(\boldsymbol{x})^{X_{h,u}} \middle| \boldsymbol{S}_h \right] \right] \\ &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}_h} \prod_{u=1}^{H} e^{-(\boldsymbol{\beta}_u.\boldsymbol{S}_h)(1-f_u^{t-1}(\boldsymbol{x}))} \right] \end{aligned}$$

since given $\boldsymbol{S}_h$, $X_{h,u} \sim \mathrm{Pois}(\boldsymbol{\beta}_u.\boldsymbol{S}_h)$ for $u = 1, \ldots, H$, and these Poisson random variables are conditionally independent. Thus,

$$\begin{aligned} f_h^t(\boldsymbol{x}) &= \mathrm{E}\left[e^{-\left(\boldsymbol{\theta} + \sum_{u=1}^{H} (1-f_u^{t-1}(\boldsymbol{x}))\boldsymbol{\beta_u}\right).\boldsymbol{S}_h} \right] \\ &= \psi_h\left(\boldsymbol{\theta} + \sum_{u=1}^{H} (1 - f_u^{t-1}(\boldsymbol{x}))\boldsymbol{\beta}_u \right) \\ &= f_h(\boldsymbol{f}^{t-1}(\boldsymbol{x})). \end{aligned}$$

Next we state the uniqueness result, in which the word 'smallest' is used in the following way. A partial ordering on vectors of dimension n is defined by $\boldsymbol{x} \leq \boldsymbol{y}$ if and only if $x_i \leq y_i$ for $1 \leq i \leq n$. Then we say that $\boldsymbol{G}$ is the smallest solution if $\boldsymbol{G} \leq \boldsymbol{x^*}$ for any other solution $\boldsymbol{x}^*$. Notice that any two vectors are not necessarily ordered, so if we have two solutions $\boldsymbol{x}_1$ and $\boldsymbol{x}_2$ that are unordered, Theorem 4.3 implies the existence of yet another solution $\boldsymbol{G}$ that is smaller than $\boldsymbol{x}_1$ and $\boldsymbol{x}_2$.

Theorem 4.3 *The vector* $\boldsymbol{G}(\boldsymbol{\theta})$ *is the smallest non-negative solution to the vector equation*

$$\boldsymbol{x} = \boldsymbol{\psi}\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - x_u)\boldsymbol{\beta}_u\right)$$

in $[0,1]^H$*. Further, when the branching process has* $R_* \leq 1$ *or is irreducible with* $\boldsymbol{\theta} \neq \mathbf{0}$*, this solution is unique. Finally, if* $\boldsymbol{\theta} = \mathbf{0}$ *then* $G_h(\mathbf{0})$ *corresponds to the probability of extinction for a branching process with one initial ancestor of type* h*.*

Proof:

The first section of the proof, to show that $\boldsymbol{G}(\boldsymbol{\theta})$ is the smallest solution to (4.1), closely follows the proof of Theorem 7.1 in Mode (1971).

First rewrite equation (4.1) as $x_h = f_h(\boldsymbol{x})$. Let $\boldsymbol{x}^*$ be a solution to this equation, and we prove by induction on t that for $t \in \mathbb{N}$

$$\boldsymbol{x}^* \geq \boldsymbol{f}^t(\mathbf{1}),$$

where $\boldsymbol{f}^t(\boldsymbol{x})$ is as defined for Lemma 4.2 and $\mathbf{1}$ is an H-vector of ones.

First, the initialisation. Since ψ_h is non-increasing,

$$\begin{aligned} x_h^* &= f_h(\boldsymbol{x}^*) \\ &= \psi_h\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - x_u^*)\boldsymbol{\beta}_u\right) \\ &\geq \psi_h\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - 0)\boldsymbol{\beta}_u\right) \end{aligned}$$

$$\begin{aligned} &= f_h(\mathbf{0}) \\ &= f_h(\boldsymbol{f}^0(\mathbf{1})) \\ &= f_h^1(\mathbf{1}) \end{aligned}$$

by Lemma 4.2. Next, assume the inductive hypothesis $x_h^* \geq \boldsymbol{f}^{t-1}(\mathbf{1})$, then

$$\boldsymbol{x}^* = \boldsymbol{f}(\boldsymbol{x}^*) \geq \boldsymbol{f}(\boldsymbol{f}^{t-1}(\mathbf{1})) = \boldsymbol{f}^t(\mathbf{1}),$$

by the lemma. Thus, by induction, $x_h^* \geq f_h^t(\mathbf{1})$ for $t \in \mathbb{N}$, and so

$$x_h^* \geq \lim_{t\to\infty} f_h^t(\mathbf{1}) = \lim_{t\to\infty} \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h(t)}\right] = G_h(\boldsymbol{\theta})$$

for $h \in \{1, \ldots, H\}$, and so $\boldsymbol{G}(\boldsymbol{\theta})$ must be the smallest solution.

Next, the second part of the theorem is proved, that this solution is unique for $R_* \leq 1$ or for an irreducible branching process with $R_* > 1$ and $\boldsymbol{\theta} \neq \mathbf{0}$. The proof is adapted from the proof of Theorem 7.2 of Mode (1971). First, we show that irrespective of the value of $\boldsymbol{x} \in [0,1]^H$,

$$\lim_{t\to\infty} f_h^t(\boldsymbol{x}) = G_h(\boldsymbol{\theta})$$

where $f_h^t(\boldsymbol{x})$ is as defined for Lemma 4.2.

This proof is split into two cases $R_* \leq 1$ and $R_* > 1$, and further assumptions about the branching process are needed in the latter case. Branching process theory says that if $R_* \leq 1$ then extinction is certain, see for example Theorem

7.1 of Mode (1972). Thus,

$$\begin{aligned}\lim_{t\to\infty} f_h^t(\boldsymbol{x}) &= \lim_{t\to\infty} \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h(t)}\boldsymbol{x}^{\boldsymbol{Z}_h(t)}\right] \\ &= \mathrm{E}\left[\lim_{t\to\infty} e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h(t)}\boldsymbol{x}^{\boldsymbol{Z}_h(t)}\right]\end{aligned}$$

by the dominated convergence theorem. Next, note that since extinction is certain, $\lim_{t\to\infty} \boldsymbol{Z}_h(t) = \mathbf{0}$ almost surely so,

$$\begin{aligned}\lim_{t\to\infty} f_h^t(\boldsymbol{x}) &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h}\right] \\ &= G_h(\boldsymbol{\theta}).\end{aligned}$$

For the same argument to work for the case $R_* > 1$, an extra assumption is required, namely

$$\lim_{t\to\infty} \exp(-\boldsymbol{\theta}.\boldsymbol{\Delta}_h(t,\omega)) = 0 \tag{4.3}$$

for all $\omega \in E^c \subseteq \Omega$, where E is the event that the branching process becomes extinct and Ω is the sample space of the branching process. Condition (4.3) can only be satisfied if $\boldsymbol{\theta} \neq \mathbf{0}$, and it is immediately satisfied if all components of $\boldsymbol{\theta}$ are strictly positive, since non-extinction implies that there will be infinitely many of at least one type of individual. If some components of $\boldsymbol{\theta}$ are zero and extinction does not occur, then condition (4.3) is satisfied if all K components of the severity vector $\boldsymbol{\Delta}_h(t)$ tend to infinity as t tends to infinity. This is true if the branching process is irreducible, which can be seen as follows.

A branching process is said to be irreducible if for every pair of types (u, v) there exists a $t \in \mathbb{N}$ such that the probability that there is at least one type v individual in generation t is strictly positive, when the branching process has

an initial ancestor of type u. If the branching process does not become extinct then there must be infinitely many of at least one type of individual, type w say. Each type w individual can be viewed as an initial ancestor of a branching process which has positive probability of producing a type v individual in t generations time, for some t, and so there must be infinitely many of each type of individual and so every type of severity must be infinite.

Thus, assuming condition (4.3) is satisfied,

$$\begin{aligned}\lim_{t\to\infty} f_h^t(\boldsymbol{x}) &= \lim_{t\to\infty} \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h(t)}\boldsymbol{x}^{\boldsymbol{Z}_h(t)}\right] \\ &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h}\middle| E\right]\mathrm{P}(E) + 0 \\ &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h}\right] \\ &= G_h(\boldsymbol{\theta}).\end{aligned}$$

Therefore, we have shown that for a branching process with $R_* \leq 1$ or with irreducibility and $\boldsymbol{\theta} \neq \mathbf{0}$,

$$\lim_{t\to\infty} \boldsymbol{f}^t(\boldsymbol{x}) = \boldsymbol{G}. \tag{4.4}$$

Next, let $\boldsymbol{G}^*$ be another solution to $\boldsymbol{G} = \boldsymbol{f}(\boldsymbol{G})$, then we show by induction on t that $\boldsymbol{f}^t(\boldsymbol{G}^*) = \boldsymbol{G}^*$. For the initialisation note that,

$$f_h^0(\boldsymbol{G}^*) = \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h(0)}(\boldsymbol{G}^*)^{\boldsymbol{Z}_h(0)}\right] = G_h^*,$$

and so $\boldsymbol{f}^0(\boldsymbol{G}^*) = \boldsymbol{G}^*$. Assume the inductive hypothesis that for $t \geq 1$, $\boldsymbol{f}^{t-1}(\boldsymbol{G}^*) = \boldsymbol{G}^*$ and note that by Lemma 4.2,

$$\boldsymbol{f}^t(\boldsymbol{G}^*) = \boldsymbol{f}(\boldsymbol{f}^{t-1}(\boldsymbol{G}^*))$$

$$\begin{aligned} &= \boldsymbol{f}(\boldsymbol{G}^*) \\ &= \boldsymbol{G}^* \end{aligned}$$

and so by induction $\boldsymbol{f}^t(\boldsymbol{G}^*) = \boldsymbol{G}^*$ for $t = 0, 1, \ldots$. However, from equation (4.4),

$$\boldsymbol{G}^* = \lim_{t\to\infty} \boldsymbol{f}^t(\boldsymbol{G}^*) = \boldsymbol{G},$$

and so $\boldsymbol{G}^* = \boldsymbol{G}$.

To show the third part of the theorem, that if $\boldsymbol{\theta} = \mathbf{0}$, then $\boldsymbol{G}(\mathbf{0})$ corresponds to the probability of extinction vector for the branching process, note that for $\boldsymbol{\theta}$ with all components strictly positive,

$$\begin{aligned} G_h(\boldsymbol{\theta}) &= \mathrm{E}[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h}|E]\mathrm{P}(E) + \mathrm{E}[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h}|E^c]\mathrm{P}(E^c) \\ &= \mathrm{E}[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h}|E]\mathrm{P}(E) \end{aligned}$$

since E^c implies at least one component of $\boldsymbol{\Delta}_h$ is infinite. Thus,

$$\begin{aligned} \lim_{\boldsymbol{\theta}\to\mathbf{0}} G_h(\boldsymbol{\theta}) &= \lim_{\boldsymbol{\theta}\to\mathbf{0}} \mathrm{E}[e^{-\boldsymbol{\theta}.\boldsymbol{\Delta}_h}|E]\mathrm{P}(E) \\ &= \mathrm{P}(E). \end{aligned}$$

When $\boldsymbol{\theta} = \mathbf{0}$, $\boldsymbol{G}(\mathbf{0}) = \mathbf{1}$ is also clearly a solution. This solution is the solution one might expect to recover, because when there are no contacts to the external population ($\boldsymbol{\alpha} = \mathbf{0}$), the probability of containment must be one. However, the smallest solution corresponds to the extinction probability for the branching process, and is therefore of greater importance and will be the one considered in the rest of this chapter. It seems unnatural to consider the outbreak to

be contained when the number of infectives has become unbounded, and so henceforth it will be assumed that the probability of containment is $\boldsymbol{G}(\boldsymbol{\alpha})$, even if $\boldsymbol{\alpha} = \mathbf{0}$.

4.2.5 Calculating the probability of containment

A possible algorithm for solving equations (4.1) for $\boldsymbol{G}(\boldsymbol{\theta})$ runs as follows.

Let $\boldsymbol{x}_0 = \mathbf{0}$ and $\boldsymbol{\psi} = (\psi_1, \ldots, \psi_H)$. For $n \in \mathbb{N}$ define

$$\boldsymbol{x}_n = \boldsymbol{\psi}\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - x_{n-1,u})\boldsymbol{\beta}_u\right).$$

To find $\boldsymbol{G}(\boldsymbol{\theta})$ sequentially calculate $\boldsymbol{x}_1, \boldsymbol{x_2}, \ldots$ until $\boldsymbol{x}_n \approx \boldsymbol{x}_{n-1}$ to the desired level of accuracy.

Here, we prove that the sequence $(\boldsymbol{x}_n)$ converges to $\boldsymbol{G}(\boldsymbol{\theta})$, and so the algorithm must converge. First we show by induction that $(\boldsymbol{x}_n)$ is non-decreasing and bounded above by $\boldsymbol{G}$.

First note that for $1 \leq h \leq H$,

$$\psi_h\left(\boldsymbol{\theta} + \sum_{u=1}^{H}\boldsymbol{\beta}_u\right) = \mathrm{E}\left[\exp\left\{-\left(\boldsymbol{\theta} + \sum_{u=1}^{H}\boldsymbol{\beta}_u\right).\boldsymbol{S}_h\right\}\right] \geq 0,$$

whence $\boldsymbol{x}_1 \geq \boldsymbol{x}_0$, where $\boldsymbol{y} \geq \boldsymbol{x}$ if and only if $y_i \geq x_i$ for all i. Next assume the inductive hypothesis that $\boldsymbol{x}_{n-1} \leq \boldsymbol{x}_n$ and note that since ψ_h is non-increasing

$$\begin{aligned}\boldsymbol{x}_n \geq \boldsymbol{x}_{n-1} \quad &\Longleftrightarrow \quad \boldsymbol{\psi}\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - x_{n,u})\boldsymbol{\beta}_u\right) \geq \boldsymbol{\psi}\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - x_{n-1,u})\boldsymbol{\beta}_u\right) \\ &\Longleftrightarrow \quad \boldsymbol{x}_{n+1} \geq \boldsymbol{x}_n.\end{aligned}$$

Therefore by induction, $(\boldsymbol{x}_n)$ is monotonic. Next, we show that $(\boldsymbol{x}_n)$ is bounded above by $\boldsymbol{G}$. Clearly $\boldsymbol{x}_0 = \mathbf{0} \leq \boldsymbol{G}$, and if we assume the inductive hypothesis $\boldsymbol{x}_n \leq \boldsymbol{G}$, then

$$\begin{aligned} \boldsymbol{G} &= \boldsymbol{\psi}\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - G_u)\boldsymbol{\beta}_u\right) \\ &\geq \boldsymbol{\psi}\left(\boldsymbol{\theta} + \sum_{u=1}^{H}(1 - x_{n,u})\boldsymbol{\beta}_u\right) \\ &= \boldsymbol{x}_{n+1} \end{aligned}$$

and so by induction $(\boldsymbol{x}_n)$ is bounded above by $\boldsymbol{G}$ for all n. For $1 \leq h \leq H$, the sequence $(x_{n,h})$ is non-decreasing and bounded above, so by the monotone sequence theorem it must converge. Given that $(x_{n,h})$ converges, it must converge to a solution to equation (4.1). Since it is bounded above by $\boldsymbol{G}$, and $\boldsymbol{G}$ is the smallest solution to this equation by Theorem 4.3, it must converge to $\boldsymbol{G}$.

Therefore this algorithm is guaranteed to converge to the solution of equation (4.1). In applications, it has been noted that remarkably few iterations are required for convergence to eight decimal places, sometimes as few as two.

4.3 Calculating the probability of containment without an intervention

In order to best understand the properties of the probability of containment, some special cases will be considered, and explored numerically. This section starts with the simplest - the case in which every household generates severity according to a known distribution. Next, a simple model for the household subepidemics is considered. The effect of having a mixture of household sizes on the model is explored and finally a multitype model for the household subepidemics is considered.

4.3.1 Household severity distribution known

Let every household generate severity according to a known distribution S with generating function ψ. This is equivalent to a model in which every household is identical and consists of a single individual with infectious period S. This case clearly demonstrates the effect of the parameters α and β upon the probability of containment.

When there is one type of infective ($K = 1$) and one type of household subepidemic ($H = 1$) with known severity distribution S, Theorem 4.1 implies that

$$G(\alpha) = \psi(\alpha + (1 - G(\alpha))\beta) \tag{4.5}$$

where individuals make internal infectious contacts at rate β, external contacts at rate α and household subepidemics produce severity according the random variable S, with generating function ψ.

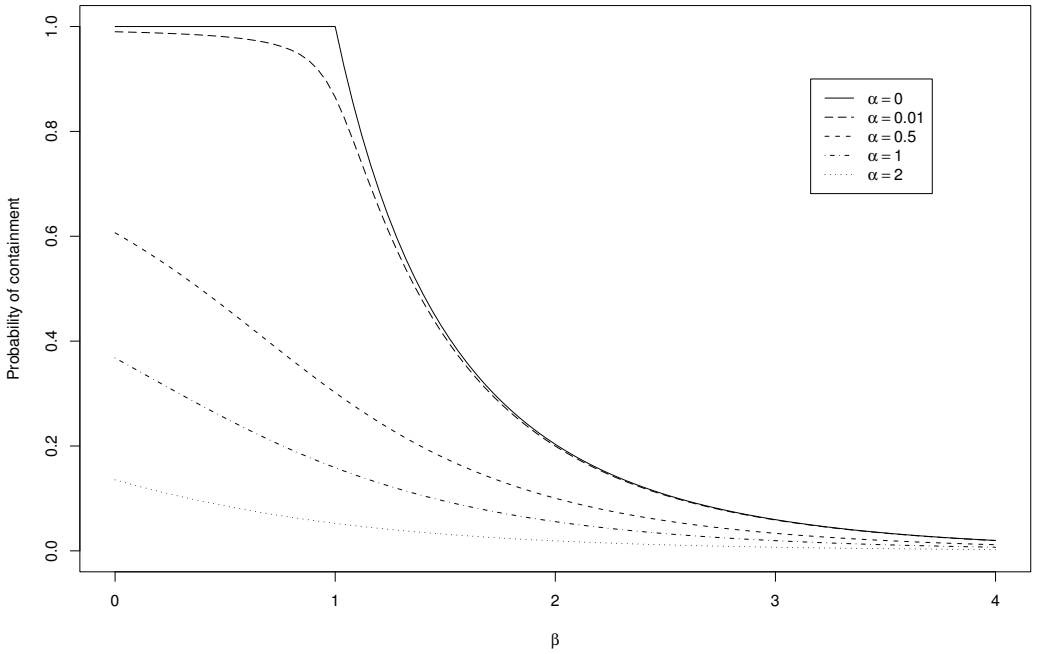

Figure 4.1: The probability of containment $G(\alpha)$ against the internal contact rate β, when $S \equiv 1$.

Figure 4.1 demonstrates the effect on the probability of containment $G(\alpha)$ of altering the infection rate β and the external contact rate α, when the household severity distribution $S \equiv 1$, and so $\psi(\theta) = e^{-\theta}$. Clearly $G(\alpha)$ is strictly decreasing in α and decreasing in β. When α is zero no external contacts are possible, and therefore the probability of containment within the target region must be one. However, the limit as α tends to zero of $G(\alpha)$ is the probability that the branching process has finitely many offspring (as discussed in Theorem 4.3). The region of figure 4.1 enclosed by the solid line $\lim_{\alpha \to 0} G(\alpha)$ and the line $G(\alpha) = 1$ (which is not shown) is unobtainable by $G(\alpha)$ for this household severity distribution. Since $\alpha = 0$ is a bounding case, it is interesting to note that for $\beta > 2$, the containment probability is small, irrespective of the value of α.

4.3.2 An SIR model for the household subepidemics

This section calculates the severity distribution of a simple SIR household subepidemic without intervention, staying with the case in which $H = K = 1$. The effect of this model on the probability of containment is explored.

Consider a household subepidemic in which individuals fall into one of three categories: susceptible, infective or removed. Let n be the number of initial susceptibles and since the household subepidemic results from a single infectious contact in the internal population, assume that there is just one initial infective in the household. Each infective has infectious period with distribution T_I and during this period makes infectious contacts with each susceptible in the household (independently) at the points of a Poisson process with rate γ. If there are n susceptibles and a single infective initially, Ball (1986) derives the generating function of the household severity to be

$$\begin{aligned} \psi(\theta) &= \mathrm{E}[\exp(-\theta S)] \\ &= \sum_{j=0}^{n} \binom{n}{j} g_j(\theta) \end{aligned}$$

where for $j = 0, \ldots, n$,

$$\sum_{w=0}^{j} \binom{j}{w} \frac{g_j(\theta)}{\phi(\theta + \gamma(n-j))^{1+w}} = 1. \tag{4.6}$$

Here $\phi(\theta) = \mathrm{E}[\exp(-\theta T_I)]$ is the generating function of the infectious period distribution. Equation (4.6) can be solved sequentially to give $g_j(\theta)$ for $j = 0, \ldots, n$. Recall that individuals in the households make internal contacts (to individuals in other households) at rate β and external contacts at rate α.

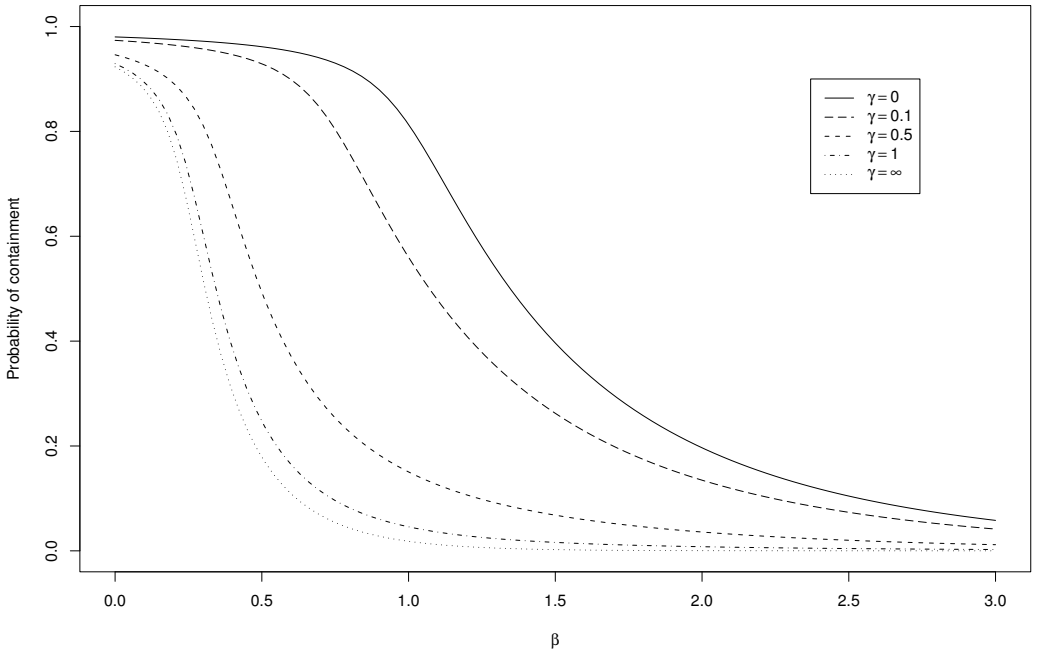

Figure 4.2: The probability of containment $G(\alpha)$ against the internal contact rate β, when $\alpha = 0.02$, $T_I \equiv 1$ and $n = 3$.

Figure 4.2 demonstrates the effect that the contact rates β and γ have on the probability of containment, for a fixed value of α, and with $T_I \equiv 1$ so that $\phi(\theta) = e^{-\theta}$. When the household contact rate γ is infinite, all of the susceptibles become infected the instant that the household does. Since the constant infectious period is the maximum under Laplace transform ordering (see section 4.4.3), this curve is a lower bound for any $G(\alpha)$ with this household size, external contact rate and expected infectious period. Notice that there is very little difference between the curves for $\gamma = 1$ and $\gamma = \infty$; and when γ is small the containment probability is much more sensitive to changes in γ. This stems from the fact that there is an upper limit on the household severity distribution corresponding to the whole household becoming infected. If n is increased then the containment probability is increasingly affected by the value

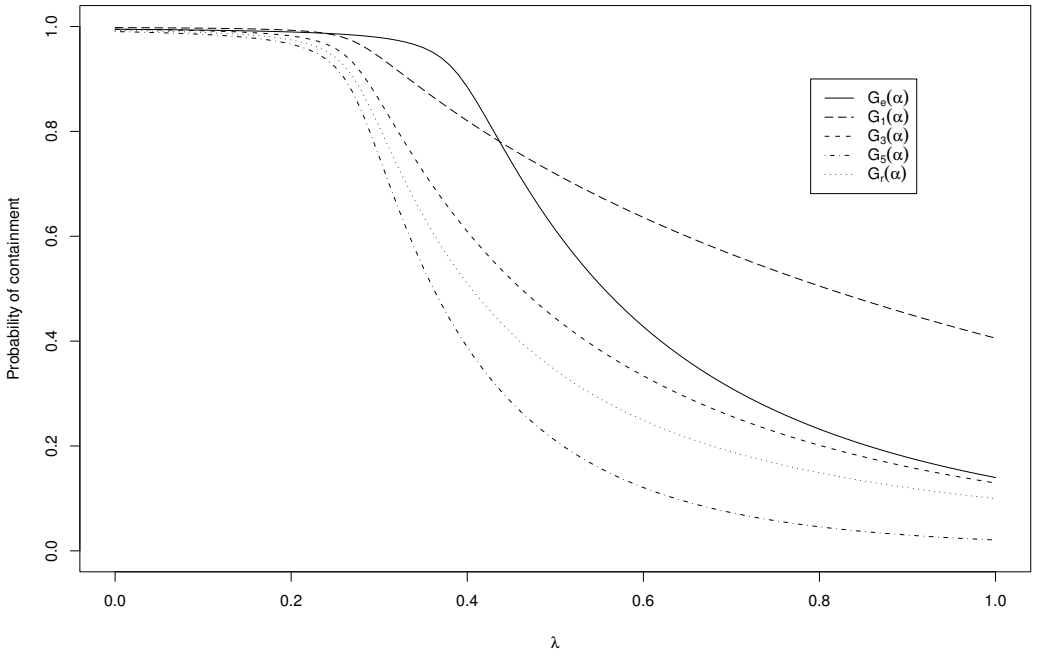

Figure 4.3: The probabilities of containment $G_e(\alpha)$, $G_r(\alpha)$ and $G_j(\alpha)$ (for $j \in \{1, 3, 5\}$) against the mixing rate λ, when $\alpha = 0.002$, $\gamma = 1$, and $T_I \equiv 1$.

of γ.

4.3.3 Mixed household sizes

Two models were compared in order to investigate the effect of mixed household sizes on the probability of containment. For comparison we consider an equal-sized households model in which all households are of size three, and a mixed households model with household sizes of one, three and five in equal amounts. In order to keep the models comparable, it is assumed in both that an infective will make contacts with susceptible individuals outside of their household with equal probability at a rate λ. Thus, in the model with equal sized households, $\beta = \lambda$, and in the mixed household size model $\beta_j = j\lambda/9$, where β_j is the rate

at which households of size j are infected for $j \in \{1, 3, 5\}$.

Figure 4.3 shows the probability of containment for the equal sized household model ($G_e(\alpha)$); the probability of containment given the branching process starts from an infectious household of size j ($G_j(\alpha)$) for the mixed sized households model; and also $G_r(\alpha)$, the probability of containment given that the mixed sized households branching process is seeded with a single infectious individual chosen uniformly at random from the population. Thus,

$$G_r(\alpha) = \frac{G_1(\alpha)}{9} + \frac{3G_3(\alpha)}{9} + \frac{5G_5(\alpha)}{9}.$$

For the branching process with equal sized households, the reproduction number is $R_* = 2.56\lambda$, and for the mixed sized households process $R_* = 3.65\lambda$. Notice that with the exception of $G_1(\alpha)$, all of the other curves fall beneath $G_e(\alpha)$, the probability of containment with equal sized households. This ties in with the fact that R_* is lower for this model. If the internal contact rate is increased in the mixed sized households process so that the two processes have the same value of R_*, then the equal sized households process has the higher containment probability only when R_* is less than approximately 1.2.

4.3.4 Two types of infective

This section compares the containment probabilities of a model that has two types of infective (called adults and children) and a model that has a single infective type. Children (type 2) are assumed to be ten times as infectious as adults (to clearly demonstrate the effect - this is not thought to be realistic). However, children make external contacts at a tenth of the rate of adults.

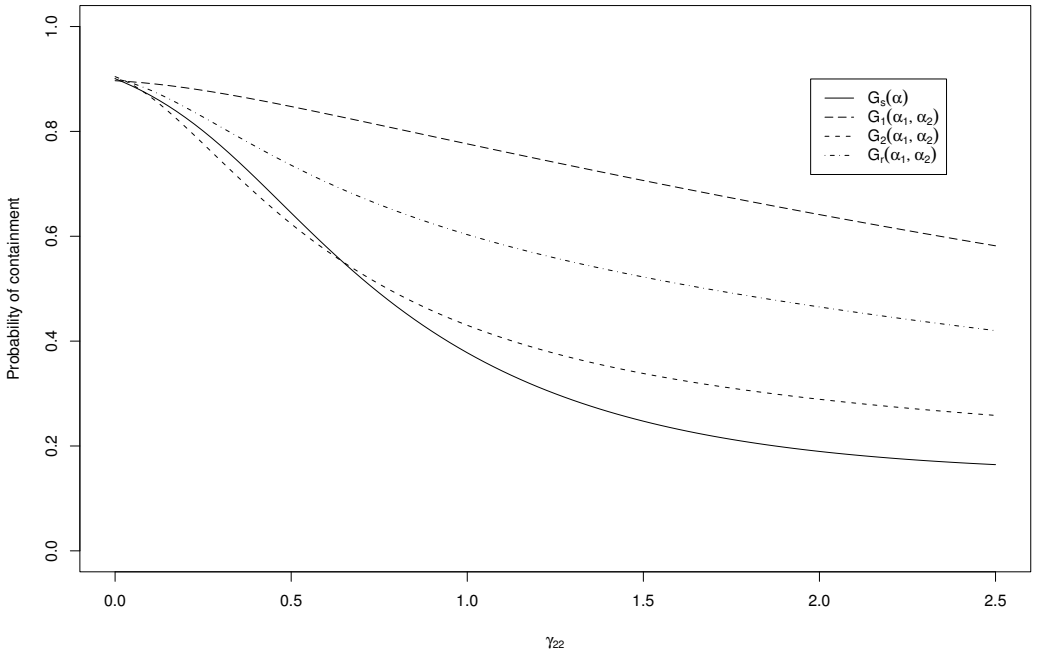

Figure 4.4: The probabilities of containment $G_s(\alpha)$, $G_r(\boldsymbol{\alpha})$ and $G_j(\boldsymbol{\alpha})$ (for $j \in \{1, 2\}$) against the household contact rate. In the two type model, households contain 2 adults and 2 children, $\boldsymbol{\alpha} = (0.1, 0.01)$, $\beta_{1,j} = 0.045$, $\beta_{2,j} = 0.45$, $\gamma_{1,j} = 0.1\gamma_{2,2} = 0.1\gamma_{2,1}$ and $T_I \equiv 1$, for $j \in \{1, 2\}$. For the one type model households are of size 4 and the parameters were chosen to be the average over the two types.

Let K be the number of types of infective, n_k be the initial number of type k susceptibles and m_k be the initial number of type k infectives, for $k = 1, \ldots, K$. Form the vectors $\boldsymbol{n} = (n_1, \ldots, n_K)$ and $\boldsymbol{m} = (m_1, \ldots, m_K)$. Write $\boldsymbol{x} \leq \boldsymbol{y}$ if $x_k \leq y_k$ for all $k = 1, \ldots, K$, and $\binom{\boldsymbol{x}}{\boldsymbol{y}}$ for $\prod_{k=1}^{K} \binom{x_k}{y_k}$. Let $\Gamma = [\gamma_{i,j}]$ be the matrix of household contact rates, and let the infectious period distribution of a type k infective have generating function $\phi_k(\theta)$. For $\boldsymbol{\theta} \in [0, \infty)^K$, Ball (1986) gives the generating function of the severity of a multitype SIR epidemic model to

be

$$\psi(\boldsymbol{\theta}) \;=\; \sum_{\mathbf{0}\le\boldsymbol{w}\le\boldsymbol{n}} g_{\boldsymbol{w}}(\boldsymbol{\theta})\binom{\boldsymbol{n}}{\boldsymbol{w}}$$

where, for $\mathbf{0} \le \boldsymbol{j} \le \boldsymbol{n}$,

$$\sum_{\mathbf{0}\le\boldsymbol{w}\le\boldsymbol{j}} \frac{g_{\boldsymbol{w}}(\boldsymbol{\theta})\binom{\boldsymbol{j}}{\boldsymbol{w}}}{\boldsymbol{\phi}(\boldsymbol{\theta}+(\boldsymbol{n}-\boldsymbol{j})\Gamma^T)^{\boldsymbol{m}+\boldsymbol{w}}} \;=\; 1,$$

where $\boldsymbol{\phi}(\boldsymbol{\theta})^{\boldsymbol{x}} = \prod_{k=1}^{K} \phi_k(\theta_k)^{x_k}$. This can again be solved sequentially to give $g_{\boldsymbol{w}}(\boldsymbol{\theta})$ for $\mathbf{0} \le \boldsymbol{w} \le \boldsymbol{n}$.

Figure 4.4 shows four versions of the probability of containment: one for a population with a single type of infective with average behaviour ($G_s(\alpha)$); two for populations seeded with an infectious adult and an infectious child ($G_1(\boldsymbol{\alpha})$ and $G_2(\boldsymbol{\alpha})$ respectively) and one for a population in which the initial infective's type is chosen at random ($G_r(\boldsymbol{\alpha}) = (G_1(\boldsymbol{\alpha})+G_2(\boldsymbol{\alpha}))/2$). The household contact rates are fixed in the following proportions as $\gamma_{2,2}$ is increased;

$$\gamma_{2,2} = \gamma_{2,1} = 10\gamma_{1,1} = 10\gamma_{1,2}.$$

When the household contact rates are very close to zero, the containment probability is lowest in a population seeded with an infectious adult. This is because the initial household forms a significant part of the branching process and adults have the highest external contact rate. As the household contact rates are increased the curves rapidly swap over, as more individuals are likely to be infected by a child and so the population seeded with a child has the lower probability of containment. Unless the household contact rate is very

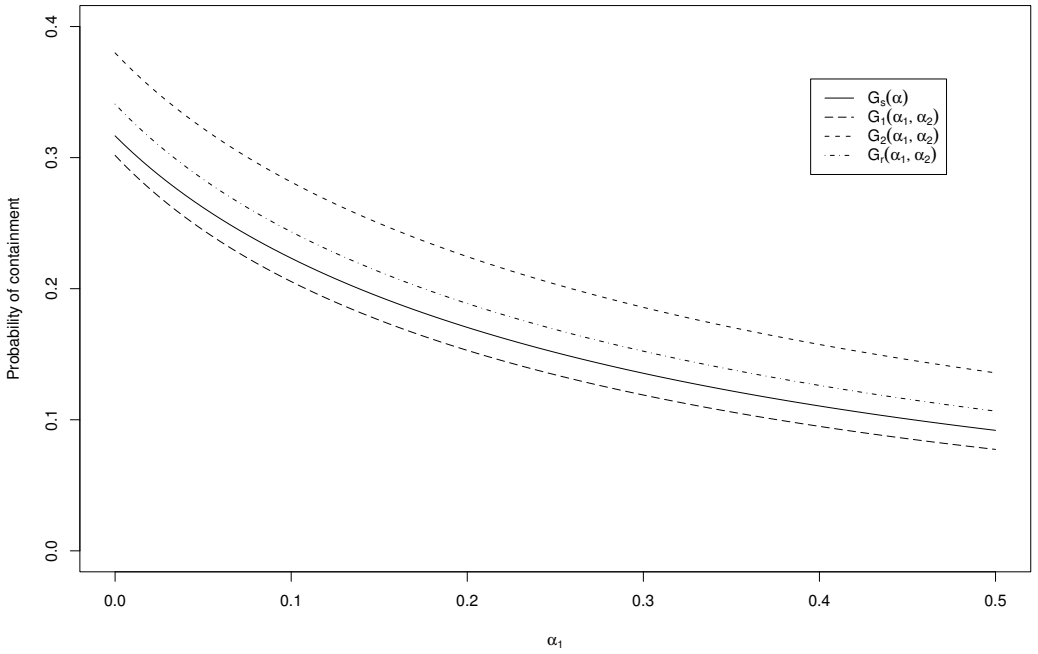

Figure 4.5: The probabilities of containment $G_s(\alpha)$, $G_r(\boldsymbol{\alpha})$ and $G_j(\boldsymbol{\alpha})$ (for $j \in \{1, 2\}$) against the external contact rate, always with $R_* = 1.8$. For the carrier model $\alpha_2 = 0.5\alpha_1$, $\beta_2 = 0.5\beta_1$ and $\boldsymbol{\gamma} = (1, 0.5)$; $T_I \equiv 1$. The single type model has the average of the two equivalent parameters in the two type model.

small, the probability of containment is lower for the population with one type of infectious individual of average infectiousness than for the population seeded with a random type of infective. This reflects the fact that the reproduction number R_* is larger for single type population when $\gamma_{2,2} > 0$. When $\gamma_{2,2} = 0$ both values of R_* are equal to $\lambda(1 + 1/10) = 0.5$. As the household contact rates tend to infinity, R_* tends to two for both models, however R_* is always larger for the single type model.

4.3.5 Asymptomatic carriers and infectives

It is a clinical feature of the influenza virus that some cases can be severe, whilst others appear to have no symptoms (Kaiser *et al.*, 2000). It is therefore assumed that infectiousness can vary between cases too (for example Longini *et al.*, 2004; Ferguson *et al.*, 2005). The simplest way to incorporate this into a model is to define two types of infectious individual, symptomatic infectives and asymptomatic carriers, each with different infectious contact rates. Once infected, an individual is symptomatic with probability 1/2 (Ferguson *et al.*, 2005), and asymptomatic otherwise.

It is possible to calculate the generating function of the household severity distribution using the formula given in section 4.3.4 by conditioning on the type of infectious behaviour each individual in the household will exhibit if infected. Thus, individuals exhibit the same type throughout their lifetime as in section 4.3.4. For example, the number of susceptibles that will be symptomatic if infected follows a binomial distribution with parameters n and 1/2.

Figure 4.5 compares the containment probability for a model with a single type of infective ($G_s(\alpha)$) with the containment probabilities for a model with asymptomatic carriers (type 2 individuals) and symptomatic infectives (type 1 individuals), as the external contact rate is increased. For $j = 1, 2$, $G_j(\boldsymbol{\alpha})$ and $G_r(\boldsymbol{\alpha})$ are the containment probabilities for this two type model, when the epidemic is seeded with a type j infective and randomly chosen infective respectively. Both models have the same reproduction number, $R_* = 1.8$ (based on Ferguson *et al.*, 2005). The curves begin at the probability that the branching process becomes extinct, and decrease towards zero. The population seeded with a symptomatic

infective is obviously least likely to be contained, and an asymptomatic seed the most likely. More interestingly, the single type population with the same value of R_* is less likely to be contained than the mixed infectiousness population with randomly chosen seed. This is because the asymptomatic carriers make the branching process more likely to become extinct in the early stages.

4.3.6 Summary of numerical illustrations

A simple version of the model defined in section 4.2.1 was considered, in which the household severity distribution was known, to demonstrate the effects of changing the external contact rate and the internal contact rate on the probability of containment. Next, a simple household model was used to demonstrate the effect of altering the household contact rate on the containment probability. Finally, the effect on the probability of containment of three ways of increasing the realism of the model was explored: mixed household structure, two types of infective, and asymptomatic carriage. Whilst having a mixture of household sizes in the model decreases the probability of containment, having a mixture of infectiousness parameters usually increases it.

4.4 Laplace transform orders

Previously we have seen how to calculate containment probabilities, which of course depend on the distribution of the household severity S, which in turn depends on the infectious period distribution T_I. This section uses a Laplace transform order to investigate such dependencies further, beginning with the model with a single household type. In particular, it is proved that the constant household severity distribution has the smallest probability of containment, for a given value of $\mathrm{E}[S]$.

4.4.1 Laplace transform orders of household severity distributions

This section is concerned with comparing household severity distributions, particularly those with equal mean, to see their effect on the containment probability for the model with a single type of household subepidemic. It is proved that a Laplace transform ordering on the household severity distributions induces a Laplace transform ordering on the total severities of the resulting branching processes, i.e. if $U \geq_{Lt} V$ then $\Delta_U \geq_{Lt} \Delta_V$, where Δ_X is the total severity of a branching process with household severities distributed according to X. The Laplace transform partial order $\geq_{Lt}$ is defined on the space of non-negative random variables by $U \geq_{Lt} V$ if and only if $\mathrm{E}[e^{-\theta U}] \leq \mathrm{E}[e^{-\theta V}]$ for all $\theta \in [0, \infty)$, assuming the expectations exist. For more details see Shaked and Shanthikumar (1994). This Laplace transform ordering implies that the containment probabilities satisfy

$$\mathrm{E}[e^{-\alpha \Delta_U}] \leq \mathrm{E}[e^{-\alpha \Delta_V}]$$

for every value of $\alpha \geq 0$.

The proof that $U \geq_{Lt} V$ implies $\Delta_U \geq_{Lt} \Delta_V$ will be structured as follows. The branching process will be constructed so that the individuals are ordered, the first $n-1$ having severity distributed according to U, and the rest having severity according to V. Then, the total severity of the branching process is decomposed about the nth individual. The effect on the total severity of changing the nth individual's severity distribution from U to V can then be isolated, and the required ordering proved.

Construct the discrete time branching process so that the individuals are uniquely numbered $0, 1, 2, \ldots$ in any way, as long as the following three conditions hold.

1. If an individual appears in an earlier generation than individual n, then its number is less than n.
2. If an individual appears in a later generation than individual n, then its number is greater than n.
3. If individual $n > 0$ has been born in the branching process, so have individuals $0, \ldots, n-1$.

Define E_n to be the event that individual n is ever born in the branching process, so if E_n does not occur, the total progeny of the branching process is less than n. For $n \in \mathbb{N}$ define $\Delta_n(X)$ to be the total severity of a branching process in which (if the individuals are ever created) individuals $0, \ldots, n-1$ have severity distributed according to U; individual n has severity distributed according to X and individuals with numbers greater than n have severity distributed according to V. Note that $\Delta_n(0)$ is the severity generated by a branching process with

severity distribution U before individual n, V after individual n and individual n generates no severity and therefore has no offspring. Define $\Delta_{X,V}$ to be the total severity generated by a branching process with severity distribution V, except for the initial ancestor which has severity distributed according to X, and define $\Delta_0(X) = \Delta_{X,V}$. For $i \in \mathbb{N}$, let $\Delta_{X,V}^{(i)}$ be i.i.d. copies of $\Delta_{X,V}$. Let $G_V(\theta) = \mathrm{E}[e^{-\theta\Delta_{V,V}}]$. Finally, assume that $U \geq_{Lt} V$. By isolating individual n and their offspring from the rest of the branching process, we see that

$$\begin{aligned}
\mathrm{E}[e^{-\theta\Delta_n(U)}] &= \mathrm{E}[e^{-\theta\Delta_n(U)}\mathbb{1}_{E_n}] + \mathrm{E}[e^{-\theta\Delta_n(U)}\mathbb{1}_{E_n^c}] \\
&= \mathrm{E}[e^{-\theta(\Delta_n(0)+\Delta_{U,V})}\mathbb{1}_{E_n}] + \mathrm{E}[e^{-\theta\Delta_n(U)}\mathbb{1}_{E_n^c}] \\
&= \mathrm{E}[e^{-\theta\Delta_n(0)}\mathbb{1}_{E_n}]\mathrm{E}[e^{-\theta\Delta_{U,V}}] + \mathrm{E}[e^{-\theta\Delta_n(U)}\mathbb{1}_{E_n^c}]
\end{aligned}$$

Let X_U denote the number of offspring produced by an individual with severity distribution U, so that $X_U \sim \mathrm{Pois}(\beta U)$. Thus,

$$\begin{aligned}
\mathrm{E}[e^{-\theta\Delta_{U,V}}] &= \mathrm{E}\left[\exp\left\{-\theta\left(U + \sum_{i=1}^{X_U}\Delta_{V,V}^{(i)}\right)\right\}\right] \\
&= \mathrm{E}\left[e^{-\theta U}\prod_{i=1}^{X_U}\mathrm{E}\left[e^{-\theta\Delta_{V,V}^{(i)}}\right]\right] \\
&= \mathrm{E}\left[e^{-\theta U}G_V(\theta)^{X_U}\right] \\
&= \mathrm{E}\left[e^{-\theta U}\mathrm{E}[G_V(\theta)^{X_U}|U]\right] \\
&= \mathrm{E}\left[e^{-(\theta+\beta(1-G_V(\theta)))U}\right] \\
&\leq \mathrm{E}\left[e^{-(\theta+\beta(1-G_V(\theta)))V}\right] \\
&= \mathrm{E}[e^{-\theta\Delta_{V,V}}]
\end{aligned}$$

Thus,

$$\begin{aligned}
\mathrm{E}[e^{-\theta\Delta_n(U)}] &= \mathrm{E}[e^{-\theta\Delta_n(0)}\mathbb{1}_{E_n}]\mathrm{E}[e^{-\theta\Delta_{U,V}}] + \mathrm{E}[e^{-\theta\Delta_n(U)}\mathbb{1}_{E_n^c}] \\
&\leq \mathrm{E}[e^{-\theta\Delta_n(0)}\mathbb{1}_{E_n}]\mathrm{E}[e^{-\theta\Delta_{V,V}}] + \mathrm{E}[e^{-\theta\Delta_n(U)}\mathbb{1}_{E_n^c}] \\
&= \mathrm{E}[e^{-\theta\Delta_n(0)}\mathbb{1}_{E_n}]\mathrm{E}[e^{-\theta\Delta_{V,V}}] + \mathrm{E}[e^{-\theta\Delta_n(V)}\mathbb{1}_{E_n^c}] \\
&= \mathrm{E}[e^{-\theta\Delta_n(V)}]
\end{aligned}$$

and so $\Delta_n(U) \geq_{Lt} \Delta_n(V)$. However, for $n = 0, 1, \ldots$, we have that $\Delta_n(U) = \Delta_{n+1}(V)$ almost surely, and so

$$\begin{aligned}
\Delta_V &= \Delta_0(V) \\
&\leq_{Lt} \Delta_0(U) \\
&= \Delta_1(V) \\
&\leq_{Lt} \Delta_1(U) \\
&\vdots \\
&\leq_{Lt} \Delta_U.
\end{aligned}$$

This is equivalent to

$$\mathrm{P}(\text{containment}|U, \alpha) \leq \mathrm{P}(\text{containment}|V, \alpha)$$

for $\alpha \in [0, \infty)$, where $\mathrm{P}(\text{containment}|X, \alpha)$ denotes the probability of containment for the branching process with household severities distributed according to X and external contact rate α.

4.4.2 Laplace transform orders of infectious period distributions

Section 4.4.1 demonstrated that if $S_1 \geq_{Lt} S_2$ then $\Delta_1 \geq_{Lt} \Delta_2$ where household severity distribution S_i gives rise to a branching process with severity Δ_i. This section discusses the equivalent property for infectious period distributions and household severities, for the household subepidemic model given in section 4.3.2 with only a single type of infective, i.e. if $T_{I,1} \geq_{Lt} T_{I,2}$ then $S_1 \geq_{Lt} S_2$. This result is proved by Lefèvre and Picard (1993) using Gontcharoff polynomials. A similar result for the final size of an epidemic was proved by Daley (1990), i.e. if $T_{I,1} \geq_{Lt} T_{I,2}$ then $Z_1 \geq_{Lt} Z_2$, where Z_i is the final size of an epidemic with infectious period distribution $T_{I,i}$.

Combining the result for the severity distributions of the household subepidemics with the result proved in section 4.4.1, we have that if $T_{I,1} \geq_{Lt} T_{I,2}$ then $\Delta_1 \geq_{Lt} \Delta_2$, which implies that

$$\mathrm{P}(\text{containment}|T_{I,1}, \alpha) \leq \mathrm{P}(\text{containment}|T_{I,2}, \alpha)$$

for $\alpha \geq 0$, where $\mathrm{P}(\text{containment}|T_{I,i}, \alpha)$ is the containment probability for a single type branching process of household subepidemics without intervention, in which the infectious periods are distributed according to $T_{I,i}$ and the external contact rate is α.

4.4.3 The constant distribution

This section considers the constant distribution, which is the maximal distribution for a given finite mean under the Laplace transform order. Recall that $U \geq_{Lt} V$ if and only if $\mathrm{E}[\exp(-\theta U)] \leq \mathrm{E}[\exp(-\theta V)]$ for every $\theta \in [0, \infty)$. The function $f(x) = \exp(-\theta x)$ is convex, and so by Jensen's inequality every random variable X satisfies $\mathrm{E}[\exp(-\theta X)] \leq \exp(-\theta \mathrm{E}[X])$, which is the Laplace transform of the constant distribution. Thus, $\mathrm{E}[X] \geq_{Lt} X$, for all non-negative random variables X with finite mean.

The result proved in section 4.4.1 then shows that $\Delta(\mathrm{E}[S]) \geq_{Lt} \Delta(S)$, where $\Delta(S)$ is the severity of a branching process with household severity distribution S. This implies that no household severity distribution with the same mean yields a larger expected total severity than the constant distribution and also the probability of containment is smallest for the constant distribution. Also, when $\alpha \to 0$, $G(\alpha)$ becomes the probability of extinction for the branching process, and so the constant household severity distribution provides the lowest probability of extinction.

Section 4.4.2 concludes that if two SIR epidemic models without intervention have infectious period distributions U and V that satisfy $U \geq_{Lt} V$ then the household severity distributions must satisfy $S(U) \geq_{Lt} S(V)$, where $S(X)$ denotes the severity distribution of an SIR epidemic with infectious period distribution X. When coupled with Jensen's inequality, this implies that $S(\mathrm{E}[T_I]) \geq_{Lt} S(T_I)$ for any non-negative infectious period distribution T_I with finite mean. Applying the result from section 4.4.1 then shows that $\Delta(S(\mathrm{E}[T_I])) \geq_{Lt} \Delta(S(T_I))$ and so the branching process with SIR household

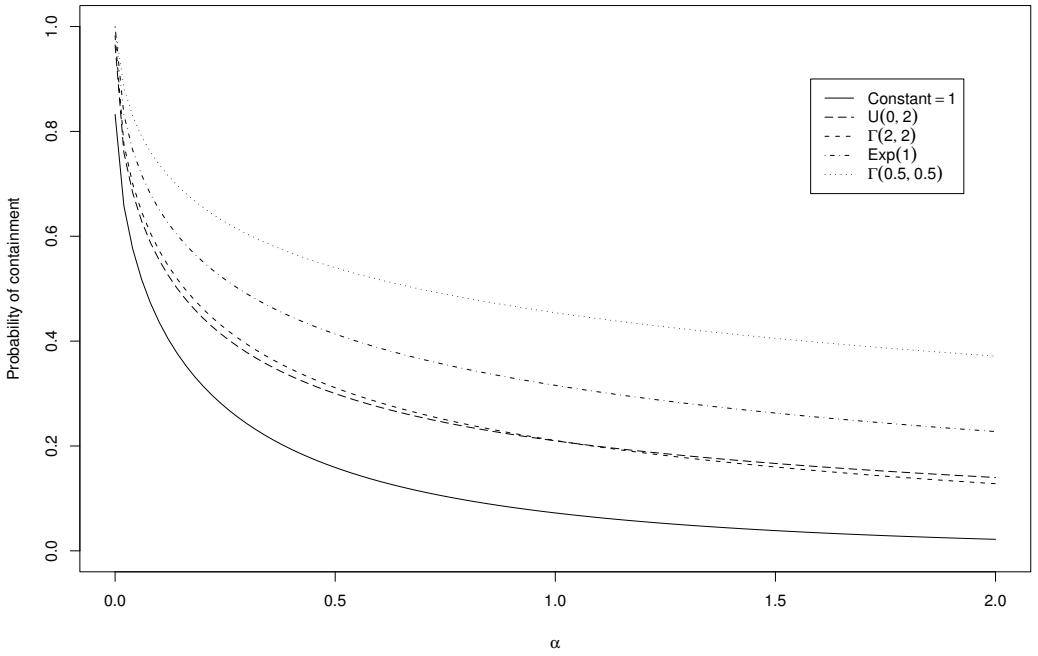

Figure 4.6: The probability of containment $G(\alpha)$ against the external contact rate α, when $\beta = 0.4$, $\gamma = 0.5$, and $\mathrm{E}[T_I] = 1$ and all households are of size 4.

subepidemics (without intervention) and constant infectious period distributions has a lower containment probability than any other infectious period distribution with this mean.

4.4.4 Examples

Figure 4.6 demonstrates the effect of the infectious period distribution on the probability of containment. The infectious period distributions given in the figure satisfy

$$1 \geq_{Lt} \mathrm{U}(0,2), \Gamma(2,2) \geq_{Lt} \mathrm{Exp}(1) \geq_{Lt} \Gamma(1/2, 1/2)$$

and so the curves appear in this order from the bottom. Notice how much variability in the containment probability can be attributed to the infectious period distribution. The smallest possible non-negative distribution (under Laplace transform ordering) is the contant zero, and this can be approached arbitrarily closely by a distribution with mean one, for example define

$$X_n = \begin{cases} n & \text{with probability } 1/n, \\ 0 & \text{with probability } 1 - 1/n, \end{cases}$$

then this distribution has mean one, and its Laplace transform tends to the Laplace transform of 0 as n tends to infinity. The distributions $\Gamma(2, 2)$ and $U(0, 2)$ are not ordered under the Laplace transform ordering and the curves representing their containment probabilities cross.

Distribution	E$[Z]$	R_*
1	1.78	1.11
U$(0, 2)$	1.56	1.02
$\Gamma(2, 2)$	1.52	1.01
Exp(1)	1.34	0.94
$\Gamma(1/2, 1/2)$	1.11	0.84

Table 4.1: The effect of the infectious period distribution on the expected household final size and R_*, for $\beta = 0.4$, $\gamma = 0.5$, E$[T_I] = 1$ and household size 4.

Table 4.1 shows the expected final size of the households and the threshold parameter for the same infectious period distributions as figure 4.6. The final size of a household subepidemic, Z, does not include the initial infective. Notice that it is not the case that the expected final sizes are all equal, despite the fact that the expected infectious periods are equal. Of the unordered infectious period distributions, the uniform has the lowest probability of containment as α approaches zero, and therefore it has a smaller probability that the branching

process is finite, and so a larger value of R_*.

4.4.5 Laplace transform orders in a multitype setting

It is possible to generalise the Laplace transform order relationships for single-type populations to hold for multitype populations. In section 4.4.2, it was noted that if the infectious period distributions satisfy $U \geq_{Lt} V$ then the respective household severities (without intervention) generated from these satisfy $S(U) \geq_{Lt} S(V)$. Lefèvre and Picard (1993) state that this can be generalised to the multitype case, so if the infectious period distributions satisfy $U_k \geq_{Lt} V_k$ $(1 \leq k \leq K)$ then the household severity distributions will satisfy $S_k(U_1, \ldots, U_K) \geq_{Lt} S_k(V_1, \ldots, V_K)$ for $1 \leq k \leq K$, where $S_k(X_1, \ldots, X_K)$ is the severity generated by a household SIR subepidemic with infectious period distributions $X_1, \ldots, X_K$ and no intervention. It is also possible to generalise the proof used for branching processes in section 4.4.1 to the multitype setting, but the notation is cumbersome and it follows the same lines as the single type case, so it will not be included here. If household severity distributions satisfy $U_h \geq_{Lt} V_h$ for $1 \leq h \leq H$, then the corresponding total severity vectors satisfy $\Delta_h(U_1, \ldots, U_H) \geq_{Lt} \Delta_h(V_1, \ldots, V_H)$ for $1 \leq h \leq H$, where $\Delta_h(X_1, \ldots, X_H)$ is the total severity generated by a H-type branching process of households, with household severity distributions $X_1, \ldots, X_H$ and initial ancestor of type h. Note that the result relating household severity distributions to containment probabilities can be applied to any model for household subepidemics (possibly including interventions), whereas the result relating infectious period distributions to household severity distributions relies on the Markov SIR household subepidemic model (without intervention) introduced in section 4.3.2.

4.5 Modelling household subepidemics with interventions

This section considers interventions at the household level, i.e. if influenza is discovered in a household (for instance by one member of the household developing symptomatic illness) then the transmission dynamics of the household change. Firstly, Markov models and then simulated models for the household subepidemics are considered. Several intervention strategies are then explored for a realistic example using simulated household subepidemics.

4.5.1 Markov household subepidemics

In order to include interventions in the household model, we require a trigger - a point in time at which to apply the intervention. It seems sensible to assume that the observation of the first symptomatic individual in the household is a suitable trigger (c.f. Ball *et al.*, 2007). Since the timing of this trigger is based on the state of the epidemic process, it can be difficult to make analytic progress if the model does not have the Markov property. Assume that the model has the Markov property, so that the transmission dynamics after the intervention depend only upon the state at the time of intervention. One disadvantage is that if the model does have the Markov property then the time spent in each state has an exponential distribution, which is not usually very realistic.

Next, a generating function for the total severity generated by a household subepidemic is derived for a general Markov model.

Let $\{X(t) : t \geq 0\}$ be a continuous time Markov process model for the household

subepidemics. Let Ω be the state space of the model, and associate with each state a function $\boldsymbol{s} : \Omega \to [0, \infty)^K$, so that if the Markov process spends a time t in state u, the severity of the household $\boldsymbol{S}$ goes up by $t\boldsymbol{s}(u)$. Let $Q = [q_{u,v}]$ be the generator matrix for the process and let ψ_u be the generating function of the household severity $\boldsymbol{S}$ given that the process starts in state $X(0) = u$. Let T_1 be the time of the first event, which has density $f_u(t) = -q_{u,u}e^{q_{u,u}t}$. So,

$$\begin{aligned}
\psi_u(\boldsymbol{\theta}) &= \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}}\middle| X(0) = u\right] \\
&= \sum_{v\in\Omega\setminus\{u\}} \int_0^\infty \Big\{ \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}}\middle| X(0) = u, X(t) = v, T_1 = t\right] \\
&\qquad\qquad \times \mathrm{P}(X(t) = v | T_1 = t, X(0) = u) f_u(t) \Big\} \,\mathrm{d}t \\
&= \sum_{v\in\Omega\setminus\{u\}} \int_0^\infty \Big\{ \mathrm{E}\left[e^{-\boldsymbol{\theta}.(t\boldsymbol{s}(u)+\boldsymbol{S})}\middle| X(0) = v\right] \\
&\qquad\qquad \times \mathrm{P}(X(t) = v | T_1 = t, X(0) = u) f_u(t) \Big\} \,\mathrm{d}t \\
&= \sum_{v\in\Omega\setminus\{u\}} \int_0^\infty e^{-t\boldsymbol{\theta}.\boldsymbol{s}(u)} \mathrm{E}\left[e^{-\boldsymbol{\theta}.\boldsymbol{S}}\middle| X(0) = v\right] \frac{q_{u,v}}{-q_{u,u}} (-q_{u,u}) e^{q_{u,u}t} \,\mathrm{d}t \\
&= \sum_{v\in\Omega\setminus\{u\}} \int_0^\infty e^{-t\boldsymbol{\theta}.\boldsymbol{s}(u)} \psi_v(\boldsymbol{\theta}) q_{u,v} e^{q_{u,u}t} \,\mathrm{d}t \\
&= \sum_{v\in\Omega\setminus\{u\}} \frac{\psi_v(\boldsymbol{\theta}) q_{u,v}}{\boldsymbol{\theta}.\boldsymbol{s}(u) - q_{u,u}}.
\end{aligned}$$

If $\boldsymbol{\theta}$ is fixed and $|\Omega|$ is finite these equations can be solved simultaneously for $\psi_u(\theta)$, for $u \in \Omega$. In practice, as the number of individuals in the household subepidemics increases, and as the possible infective behaviour becomes more complex, the size of the state space Ω becomes very large, and so solutions to these equations are time consuming to compute.

4.5.2 Simulated household subepidemics

As the model for the household subepidemic is made more realistic and more complicated, it becomes increasingly difficult to make analytic progress towards finding the generating function of the household severity. It is however possible to find an approximation for the generating function by simulating the household severity distribution, which can be done very quickly and easily for even very complicated models, for example models that include several types of infective, each of which undergoes several phases of infection. This approach is much better than simulating the whole branching process of households as it can be done much more rapidly and robustly. Simulating a branching process with a reproduction number close to one is difficult because some realisations may take a very long time to die out and therefore a very large number of calculations need to be performed to determine whether or not extinction occurs.

Another situation in which it is appropriate to approximate the generating function from a sample from the distribution of household severities arises when performing inference on household epidemic data. Cauchemez *et al.* (2004) use Markov Chain Monte Carlo methods to analyse purely household based data to estimate the household transmission parameters for influenza. In order to obtain estimates of the infectiousness, it is also necessary to impute the infection times, and therefore implicitly the household severity. These samples from the household severity distribution can then be used to estimate the generating function of the household severity. This can then be used with estimates for the internal and external transmission parameters to calculate the containment probability, without needing to simulate the entire branching process - which can be difficult if the threshold parameter is close to unity.

If there are r samples $\boldsymbol{S}_1, \ldots, \boldsymbol{S}_r$ from a household severity distribution with K kinds of severity then a generating function $\psi(\boldsymbol{\theta})$ can be formed simply by summing the appropriate functions of the samples.

$$\psi(\boldsymbol{\theta}) = \sum_{i=1}^{r} \frac{\exp(-\boldsymbol{\theta}.\boldsymbol{S}_i)}{r}$$

4.5.3 Influenza in rural Thailand

Ferguson *et al.* (2005) use household epidemic data to determine estimates of influenza natural history parameters and distributions. These estimates are used to construct a detailed model for influenza transmission in Thailand, which is then simulated to determine the effectiveness of several intervention strategies aimed at eradicating the disease from Thailand. They do not model any transmissions out of the region. In this section, the parameter estimates obtained by Fergusson *et al.* are used to simulate the household severity distribution for several possible interventions at the household level. The effectiveness of each intervention strategy is then quantified by the effect on the probability of containment. Finally, a suitable distribution for the initial number of infectious households is arrived at.

Household size	Proportion	Household size	Proportion
1	0.105	6	0.030
2	0.175	7	0.015
3	0.230	8	0.005
4	0.270	9	0.004
5	0.165	10	0.001

Table 4.2: The household size distribution of Thailand.

In contrast to many other modelling papers, Ferguson *et al.* (2005) have a constant length infectious period during which infectiousness varies. This is

simple to incorporate into our model if the household severity is defined to be the integral of the present household infectiousness level over the entire period of the household subepidemic. In fact, this simplifies things somewhat, as it is now sufficient to consider just this single type of severity. Again following Ferguson *et al.*, after infection each individual undergoes a latent period with length distributed according to 0.5 days plus a Weibull distribution with power parameter 2.21 and scale parameter 1.1. It is assumed that 50% of infections are severe (strongly symptomatic) and these are twice as infectious as those that are non-severe. Infectiousness for severe cases varies according to the density of a lognormal distribution with parameters -0.72 and 1.8 truncated at 10 days and then renormalised; denote this density by κ. The probability of a household member avoiding infection in the first t days of infectiousness from a severe case is assumed to be

$$\exp\left(-\int_0^t \frac{0.94}{n^{0.8}}\kappa(u)\mathrm{d}u\right)$$

where n is the number of individuals in the household. Table 4.2 shows the distribution of household sizes.

The internal contact rate β was chosen to give a value of R_* equal to 1.8 to match the paper, which has more than two levels of mixing. Following Ferguson *et al.* (2005), the simulations were actually performed in a discretisation of the above model, in which all events that occur in $((t-1)/4, t/4]$ actually occur at time $t/4$, for $t \in \mathbb{N}$. This does not effect the severity produced by the household (since infectious periods have constant length 10 days) except by changing slightly the time at which the intervention (if there is one) is applied.

Interventions

The following five intervention strategies are considered.

1. No intervention,
2. Household isolation,
3. Household prophylaxis,
4. Blanket prophylaxis,
5. Social distancing.

Again following Ferguson *et al.* (2005), in the household isolation and household prophylaxis intervention strategies, severe infections exhibit healthcare-seeking behaviour 0.25 days after the onset of symptoms, assumed to coinside with the start of the infectious period, and at this point the intervention is triggered with probability 0.9. In the household isolation intervention strategy it is assumed that no more internal or external infections can emerge from an isolated household after the intervention, and therefore any further household infections and household severity are inconsequential. In the household prophylaxis intervention strategy, each individual is given a course of antivirals with probability 0.9. Ferguson *et al.* (2005) assume that a course of the antiviral drug Oseltamivir (Tamiflu) will reduce infectiousness by 60%, reduce susceptibility by 30% and reduce the probability of a severe infection by 65%. In the blanket prophylaxis intervention, 90% of the population is given a course of antivirals at the outset. Finally, in the social distancing intervention the internal contact rate is decreased so that R_* is reduced from 1.8, to the threshold level of one, at which the extinction of the branching process becomes certain.

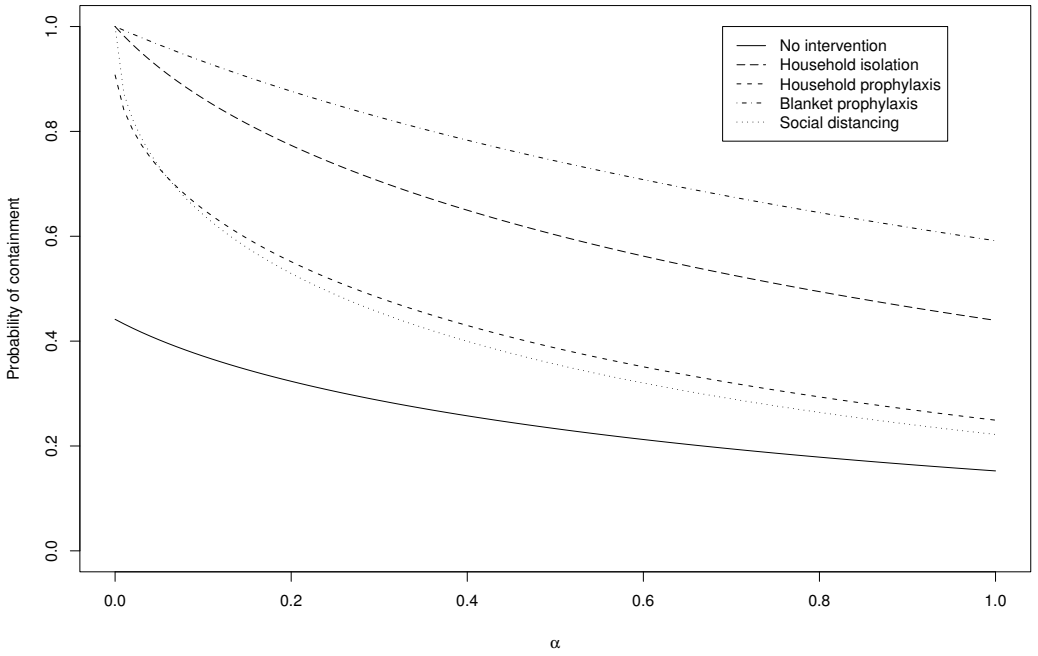

Figure 4.7: The probability of containment against the external contact rate α for five intervention strategies with 10,000 simulations of each of the 10 household sizes.

Figure 4.7 shows the probability of containment for the intervention strategies described above, and table 4.3 gives the R_* values. The household prophylaxis strategy and the social distancing strategy give similar improvements in the probability of containment. It is interesting to note that for some values of α the household prophylaxis strategy outperforms the social distancing strategy, despite the fact that it has failed to reduce R_* below one. This is because the household prophylaxis strategy reduces infectiousness and therefore decreases the number of external contacts per household, whereas it has been assumed that the social distancing strategy has no effect on the external contact rate.

The household isolation strategy is the best possible household based intervention with this set of trigger assumptions, as no contacts are assumed to

Intervention Strategy	R_*
No intervention	1.80
Household isolation	0.71
Household prophylaxis	1.05
Blanket prophylaxis	0.42
Social distancing	1.00

Table 4.3: The threshold parameter R_* after intervention for five intervention strategies for the household simulation model.

be made after the intervention is triggered. Despite this, the blanket prophylaxis strategy has a substantially lower value of R_*. This substantial difference in threshold parameters is not as strongly reflected in the probability of containment. This is probably due to the fact that approaching a containment probability of one becomes increasingly difficult.

Computationally, these results were very rapid to produce - 10,000 simulations of each of the 10 possible household subepidemics were produced in about 45 minutes to obtain an estimate for the severity function. The algorithm to calculate the probability of containment using these simulations usually converges in two to five iterations, and takes at most a few seconds. To produce 10,000 simulations of such a complicated branching process model using the same computing resources would take considerably longer - particularly as many of the threshold parameters in table 4.3 are extremely near to one.

4.5.4 Initial phase

It may be unrealistic to assume that interventions can be applied to the earliest generations of the branching process, as they may not even contain any symptomatic cases. In section 4.5.3 it is assumed that the intervention can be applied to the single initially infected household in the branching process. A

more realistic approach is to seed the branching process with the number of infectious households generated during an initial phase without intervention.

Let X denote the number of infectious households with which the branching process is seeded. We will take X to be the number of infectious households produced by the first generation in which the cumulative number of observed cases exceeds 5. The distribution of X was found by the following method.

Firstly 200,000 household subepidemics were simulated, and the severity and number of observed cases was recorded in each case. Recall that 90% of the symptomatic cases are assumed to be observed. Next, 10,000 realisations of the branching process were simulated up to the first generation in which the cumulative number of observed cases exceeded 5, and the severity of this generation was recorded. If the branching process became extinct before this point, then that realisation was discarded. For each of the 5,240 successful realisations of the branching process severity, 10 observations of the offspring distribution were simulated and contributed towards the distribution of X. The probability of containment was then taken to be

$$\sum_{i=0}^{\infty} G(\alpha)^i \mathrm{P}(X = i).$$

Figure 4.8 shows the probability of containment given that five cases have been observed, after which the intervention is applied. Obviously increasing the number of seeds makes the probability of containment much smaller, however note that there is also a small probability that $X = 0$, and so very small probabilities of containment will increase. Without intervention, the probability of containment is now very small, in contrast to when the branching process

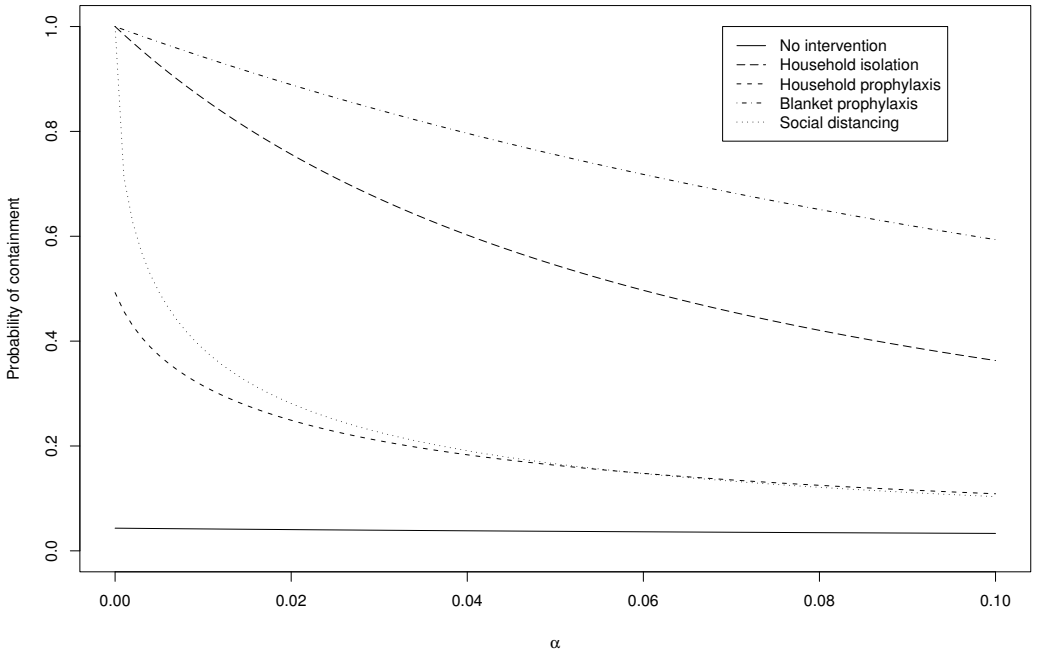

Figure 4.8: The probability of containment for five intervention strategies, when the branching process is seeded with a random number of infectious households.

was seeded with a single infective. This highlights the importance of good case surveillance, and the need to apply the intervention as soon as possible after the first few cases are observed. Household prophylaxis and social distancing only appear to be very effective for small external contact rates. Household isolation and blanket prophylaxis remain effective for more values of α, but it is not long before the probability of containment drops below 0.5.

4.6 Conclusion and extensions

Halting an emerging disease like avian influenza in its early stages is vital to prevent a pandemic. Mathematical models such as the ones developed here provide a way to quantify the risks and assess the effectiveness of public health policies before the event. This chapter has developed a method to find the probability that an intervention will successfully contain an outbreak of pandemic influenza in humans. A branching process of households was used to model the spread of infection through a population. Whilst the intervention was considered to be effective within this population, the possibility that the infection was transported outside this region was modelled. Several effects on the probability of containment were then explored, without interventions.

It was found that if two infectious period distributions were ordered under the Laplace transform ordering, then their probabilities of containment had the reverse ordering. If a mixture of household sizes was introduced into the population this reduced the probability of containment. If a mixture of infectiousness parameters was introduced into the model, this increased the probability of containment.

Simulating the household severity distributions was found to be quicker and much more flexible than using a Markov model. Several interventions were considered with a household model based on the paper by Ferguson *et al.* (2005), and blanket prophylaxis and household isolation were found to be more effective than household prophylaxis and social distancing. Finally, an initial phase without intervention was added to the model and this massively reduced the range of external contact rates for which the interventions were effective. This

initial phase without intervention was assumed to be over for the generation after the first generation in which the total number of observed cases exceeds five. This number of cases needed to initiate the intervention strategy could be investigated further. If possible it should optimise the probability of containing an emerging pandemic compared with the costs associated with an unnecessary intervention caused by false detections and strains that are yet to develop the ability to transmit efficiently between humans.

Chapter 5

Conclusion and extensions

This chapter briefly summarises the purpose and main results of each chapter of the thesis as well as suggesting some possible extensions.

5.1 Asymptomatic carriers

Chapter 2 of this thesis considers diseases in which a proportion of infected individuals never develop symptoms, or develop only very mild symptoms, and so are never detected. Such individuals are called asymptomatic carriers and can significantly increase the spread of a disease. Asymptomatic carriers make it very difficult to be certain that a disease has died out, even if no cases have been detected recently. The aim of chapter 2 is to calculate the probability the epidemic has died out given that no symptomatic cases have been observed for a certain amount of time.

Throughout chapter 2 it is assumed that at time zero the distribution of the

number of initial infectives is known. In practice, it is hard to know how this distribution might be obtained. It would be interesting to explore the effect that the initial distribution has on the probability the epidemic is over, particularly for the stopping time version of the problem.

There are some interesting inference problems relating to asymptomatic carriers, for instance developing a model with which it is possible to test for the presence of asymptomatic carriage from temporal data on case numbers. Estimating the proportion of individuals that are asymptomatic could also be investigated.

5.2 Modelling the effects of a delay in intervention

Chapter 3 investigates the effect of modelling a delay between observing an infected individual in a household and applying an intervention to that household. The expected effective severity is defined to be the expected sum of the infectious periods in a household, up to the time that the intervention is applied, and this is calculated for a household subepidemic in a two level mixing model. The expected effective severity is proportional to the reproduction number R_*, which can be used to assess the effectiveness of an intervention.

Chapter 3 could be extended in many ways. Interventions that are not perfectly effective could be considered, as could different distributions for the length of the delay before the intervention is applied. During the early stages of an epidemic, vaccines or interventions like administering antivirals are likely to be in short supply, and this model allows them to be given to households in which the epidemic has already died out. This raises the question in what proportion of the households the intervention is ultimately totally ineffective, and how could these households be identified.

5.3 Evaluating the probability of containment for pandemic influenza

Chapter 4 of this thesis develops a model to assess whether an outbreak of an emerging disease can be contained by an intervention to the region from which it emerged. This problem is motivated by the study of pandemic influenza in humans. A multitype branching process of households is used to model the spread of the disease in the region in which the intervention is fully effective, and a Poisson process of external contacts is used to model the transmission of the disease to outside this region. The containment probability is derived and shown to be unique for a very general model, in which the household transmission model is not specified. This allows a variety of different intervention strategies targeted at the household level to be compared.

The effect on the probability of containment of changing various aspects of the model was then explored numerically. It was found that if a mixture of household sizes was included in the model this reduced the containment probability, however, if individuals were allowed a mixture of levels of infectiousness, this increased the containment probability. It was proved that if two infectious period distributions were ordered under the Laplace transform ordering, then their probabilities of containment had the reverse ordering.

It was found that simulating the household severity distribution was easier and more flexible than using a Markov process model, and was much faster than simulating the whole branching process of households. Finally, a specific household transmission model was considered based on Ferguson *et al.* (2005) for a selection of intervention strategies. It was found that blanket prophylaxis and

household isolation were more effective than household prophylaxis and social distancing, and a more appropriate number of initially infected households was simulated.

The models and methods used in chapter 4 could be extended in several ways. It is assumed that given a household's severity, the number of internal contacts follows a Poisson distribution, and this assumption could be relaxed. This would allow more variation in the number of infections an individual could make, and so the model would better capture so called 'superspreaders' that infect a very large number of individuals. Many other household severity models could be explored. Forward contact tracing could be included in the simulated household model by assuming that a proportion of a household's offspring will be given antivirals some time after they were created. Backward contact tracing could be incorporated into the household model by assuming that a household is investigated some period of time after making an infectious contact. A more thorough investigation could be conducted into the appropriate number of infectious households with which to seed the branching process. Mixtures of intervention strategies could also be considered.

Although the model used in chapter 4 was developed to model an emerging influenza pandemic in humans, it is very flexible and could be applied to other emerging infectious diseases.

Chapter 6

Appendices

Appendix A

An appendix to show that for the asymptomatic carriage epidemic model the size of the state space $E_{n,i,c}$ is equal to

$$|E_{n,i,c}| = (n+1)(i+1)(c+1) + \frac{n(n-1)(i+c+1)}{2} + \frac{n(n+1)(n+2)}{6}.$$

Let

$$e_j = |\{(j, y, z) \in E_{n,i,c}\}|$$

so that

$$|E_{n,i,c}| = \sum_{j=0}^{n} e_j.$$

Clearly $e_n = (i+1)(c+1)$ because given only that no infections have occurred, it is known that the number of infectives is between 0 and i and the number of carriers is between 0 and c (inclusive).

Next note that,

$$e_{n-1} = e_n + i + 1 + c + 1$$

since the pair representing the numbers of infectives and carriers can be all of the pairs above; plus $c+1$ pairs of the form $(i+1, j)$ for $j = 0, \ldots, c$ and $i+1$ pairs of the form $(j, c+1)$ for $j = 0, \ldots, i$.

In fact for $k = 1, \ldots, n$,

$$e_{n-k} = e_{n-k+1} + i + 1 + c + 1 + k - 1$$

since there are now $c+1$ extra pairs of the form $(i+k, j)$ for $j = 0, \ldots, i$; $i+1$ extra pairs of the form $(j, c+k)$ for $j = 0, \ldots, c$; and $k-1$ extra pairs of the form $(i+j, c+k-j)$ for $j = 1, \ldots, k-1$. It is easy to show by induction on k that

$$e_{n-k} = (i+1)(c+1) + k(i+c+1) + \frac{k(k+1)}{2}.$$

Initialisation:

$$e_n = (i+1)(c+1)$$

as required.

Inductive Hypothesis:

$$e_{n-k} = (i+1)(c+1) + k(i+c+1) + \frac{k(k+1)}{2}.$$

Inductive Step:

$$\begin{aligned} e_{n-(k+1)} &= e_{n-k} + i + c + 1 + k + 1 \\ &= (i+1)(c+1) + k(i+c+1) + \frac{k(k+1)}{2} + i + c + 1 + k + 1 \\ &= (i+1)(c+1) + (k+1)(i+c+1) + \frac{(k+1)(k+2)}{2} \end{aligned}$$

as required.

It remains only to find

$$\begin{aligned} |E_{n,i,c}| &= \sum_{k=0}^{n} e_{n-k} \\ &= \sum_{k=0}^{n} (i+1)(c+1) + k(i+c+1) + \frac{k(k+1)}{2} \\ &= (n+1)(i+1)(c+1) + \left(i + c + \frac{3}{2}\right) \sum_{k=0}^{n} k + \frac{1}{2} \sum_{k=0}^{n} k^2 \\ &= (n+1)(i+1)(c+1) + \left(i + c + \frac{3}{2}\right) \frac{n(n+1)}{2} + \frac{n(n+1)(2n+1)}{12} \\ &= (n+1)(i+1)(c+1) + \frac{n(n+1)(i+c+1)}{2} + \frac{n(n+1)(n+2)}{6}. \end{aligned}$$

This completes the proof.

Appendix B

Lemma 2.1 *For any distinct real numbers $x_1, \ldots, x_n$ $(n > 1)$,*

$$\sum_{j=1}^{n} \prod_{\substack{k=1 \\ k \neq j}} \frac{1}{x_j - x_k} \quad = \quad 0$$

Proof:

Without loss of generality we may assume that the real numbers $x_1, \ldots, x_n$ are positive, since we can apply the result to the list $x_1 + \lambda, \ldots, x_n + \lambda$ for any λ, and the λs will cancel to give the more general result.

Let $Y_i \sim \text{Exp}(x_i)$ for $i = 1, \ldots, n$ be independent random variables. From page 203 of Rényi (1970) for $n \in \mathbb{N}$, the random variable

$$S_n = \sum_{i=1}^{n} Y_i$$

has probability density function

$$g_n(t) = (-1)^{n-1} b_1 \ldots b_n \sum_{k=1}^{n} \frac{e^{-b_k t}}{\prod_{i \neq k} b_k - b_i}$$

for $t > 0$. Now let $x = \min\{x_1, \ldots, x_n\}$. If $X_1, \ldots, X_n$ are i.i.d. $\text{Exp}(x)$ random variables then

$$R_n = \sum_{i=1}^{n} X_i$$

is a $\Gamma(n, x)$ random variable with probability density function

$$f_n(t) = \frac{x^n t^{n-1} e^{-xt}}{(n-1)!}$$

for $t > 0$.

Since the X_i and Y_i are exponentially distributed and $x \leq x_i$ (for $i = 1, \ldots, n$) then, for all $\epsilon > 0$,

$$\mathrm{P}(R_n < \epsilon) > \mathrm{P}(S_n < \epsilon)$$

which implies that

$$\int_0^\epsilon f_n(t)\mathrm{d}t > \int_0^\epsilon g_n(t)\mathrm{d}t.$$

Since this is true for all $\epsilon > 0$ and $f_n(t), g_n(t) \geq 0$;

$$\lim_{\epsilon \to 0} f_n(\epsilon) \geq \lim_{\epsilon \to 0} g_n(\epsilon) \geq 0.$$

But for $n > 1$,

$$\lim_{\epsilon \to 0} f_n(\epsilon) = 0$$

follows from the definition of $f_n(t)$. Thus,

$$\begin{aligned} 0 &= \lim_{\epsilon \to 0} g_n(\epsilon) \\ &= \lim_{\epsilon \to 0} (-1)^{n-1} x_1 \ldots x_n \sum_{k=1}^{n} \frac{e^{-x_k \epsilon}}{\prod\limits_{i \neq k} x_k - x_i} \\ &= (-1)^{n-1} x_1 \ldots x_n \sum_{k=1}^{n} \frac{1}{\prod\limits_{i \neq k} x_k - x_i} \end{aligned}$$

and since $x_i > 0$ for $i = 1, \ldots, n$, the result follows.

Appendix C

Lemma 6.1 *Let Q be a substochastic $d \times d$ matrix in which for all states x there exists a state y and a $k \in \mathbb{N} \cup \{0\}$ such that the probability of going from x to y in k steps is strictly positive, and the state y satisfies $\sum_{j=1}^{d} q_{y,j} < 1$. Then,*

$$\sum_{t=0}^{\infty} Q^t = (\mathbf{1} - Q)^{-1}.$$

Proof: (following Young (1988, P73))

Let $q_{i,j}$ represent the (i,j)th entry of Q and let $q_{i,j}^{(k)}$ be the probability of going from i to j in k steps. The states not represented in Q are absorbing states and so $q_{i,j}^{(k)}$ is the (i,j)th entry in the matrix Q^k. The conditions of the theorem imply that for each row i in Q there exists a $k(i)$ such that $\sum_{j=1}^{d} q_{i,j}^{(k(i)+1)} < 1$. Define $K = 1 + \max\{k(i) : i = 1, \ldots, d\}$, and so every row in Q^K will sum to strictly less than one. Let $\|\cdot\|$ be the norm

$$\|\boldsymbol{x}\| = \sum_{i=1}^{d} |x_i|$$

on $\mathbb{R}^d$ and define a matrix norm $\|Q\| = \sup\{\|\boldsymbol{x}Q\| : \boldsymbol{x} \in \mathbb{R}^d, \|\boldsymbol{x}\| \leq 1\}$. Since every row of Q^K has sum strictly less than one, we have that $\|Q^K\| < 1$. First we show that the sequence $(\boldsymbol{x}(1 + Q + Q^2 + \ldots + Q^n))_{n=1}^{\infty}$ converges and then that $1 + Q + Q^2 + \ldots + Q^n \to (1 - Q)^{-1}$ as $n \to \infty$.

If the sequence $(\boldsymbol{x}(1 + Q + Q^2 + \ldots + Q^n))_{n=1}^{\infty}$ is a Cauchy sequence, then since $\mathbb{R}^d$ is complete the sequence must converge, so it suffices to prove that it is Cauchy.

For $m > n > K$,

$$\begin{aligned}
&\|\boldsymbol{x}(1+Q+Q^2+\ldots+Q^m)-\boldsymbol{x}(1+Q+Q^2+\ldots+Q^n)\| \\
&\qquad = \|\boldsymbol{x}(Q^{n+1}+\ldots+Q^m)\| \\
&\qquad \leq \|\boldsymbol{x}Q^{n+1}\|+\ldots+\|\boldsymbol{x}Q^m\| \\
&\qquad \leq \|\boldsymbol{x}\|\|Q^{n+1}\|+\ldots+\|\boldsymbol{x}\|\|Q^m\| \\
&\qquad \leq \|\boldsymbol{x}\|\sum_{a=n+1}^{\infty}\|Q^a\| \\
&\qquad \leq \|\boldsymbol{x}\|\sum_{a=NK}^{\infty}\|Q^a\|
\end{aligned}$$

where $N = \min\{c \in \mathbb{N} : cK \leq n+1 < (c+1)K\}$. Thus,

$$\begin{aligned}
&\|\boldsymbol{x}(1+Q+Q^2+\ldots+Q^m)-\boldsymbol{x}(1+Q+Q^2+\ldots+Q^n)\| \\
&\qquad \leq \|\boldsymbol{x}\|\sum_{b=N}^{\infty}\|Q^{Kb}\|+\|Q^{Kb+1}\|+\ldots+\|Q^{Kb+K-1}\| \\
&\qquad \leq \|\boldsymbol{x}\|\sum_{b=N}^{\infty}\|Q^{Kb}\|(1+\|Q\|+\ldots+\|Q^{K-1}\|)
\end{aligned}$$

since $\|Q^{c+d}\| \leq \|Q^c\|\|Q^d\|$. So,

$$\begin{aligned}
&\|\boldsymbol{x}(1+Q+Q^2+\ldots+Q^m)-\boldsymbol{x}(1+Q+Q^2+\ldots+Q^n)\| \\
&\qquad \leq \|\boldsymbol{x}\|(1+\|Q\|+\ldots+\|Q^{K-1}\|)\sum_{b=N}^{\infty}\|Q^K\|^b \\
&\qquad = \frac{\|\boldsymbol{x}\|(1+\|Q\|+\ldots+\|Q^{K-1}\|)\|Q^K\|^N}{1-\|Q^K\|} \qquad (6.1) \\
&\qquad \to 0
\end{aligned}$$

as $n \to \infty$ with $m > n$, since $N \to \infty$ as $n \to \infty$. Thus the sequence $(\boldsymbol{x}(1+Q+Q^2+\ldots+Q^n))_{n=1}^{\infty}$ is a Cauchy sequence in the complete space $\mathbb{R}^d$

and therefore it must converge to a limit. Call this limit $\boldsymbol{x}T \in \mathbb{R}^d$. Clearly T is a linear operator and letting $m \to \infty$ in (6.1) yields

$$\|\boldsymbol{x}T - \boldsymbol{x}(1 + Q + \ldots + Q^n)\| \leq \frac{\|\boldsymbol{x}\|(1 + \|Q\| + \ldots + \|Q^{K-1}\|)\|Q^K\|^N}{1 - \|Q^K\|}, \quad (6.2)$$

which shows that $T - (1 + Q + \ldots + Q^n)$ is a bounded linear operator and so T is also a bounded linear operator. Now (6.2) implies that

$$\|T - (1 + Q + \ldots + Q^n)\| \leq \frac{(1 + \|Q\| + \ldots + \|Q^{K-1}\|)\|Q^K\|^N}{1 - \|Q^K\|}$$

and letting $n \to \infty$ (which implies $N \to \infty$), shows that $1 + Q + \ldots + Q^n \to T$ as $n \to \infty$. It remains to show that $(1 - Q)^{-1} = T$.

For $x \in \mathbb{R}^d$, the continuity of $1 - Q$ gives

$$\begin{aligned}
\boldsymbol{x}(1 - Q)T &= \boldsymbol{x}(1 - Q) \lim_{n\to\infty} (1 + Q + Q^2 + \ldots + Q^n) \\
&= \lim_{n\to\infty} \boldsymbol{x}(1 - Q)(1 + Q + Q^2 + \ldots + Q^n) \\
&= \lim_{n\to\infty} \boldsymbol{x} - \boldsymbol{x}Q^{n+1} \\
&= \boldsymbol{x}
\end{aligned}$$

since from the definition of $\|Q\|$,

$$\begin{aligned}
\|\boldsymbol{x}Q^{n+1}\| &\leq \|\boldsymbol{x}\|\|Q^{n+1}\| \\
&\leq \|\boldsymbol{x}\|\|Q\|^{n+1} \\
&\to 0
\end{aligned}$$

as $n \to \infty$.

Chapter 7

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